#16

BY HAND DELIVERY
Date of Delivery: December 1, 2006 Attorney Docket No.: 27499-502 PTE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	U.S. Patent No.: RE38,506 E, issued April 20, 2004; Reissue of 5,369,108, issued November 29, 1994
To:	Ronald Breslow, Paul A. Marks, Richard A. Rifkind, Branko Jursic
Assignee:	Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York
Title:	Potent Inducers of Terminal Differentiation and Methods of Use Thereof

MAIL STOP HATCH-WAXMAN PTE
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 223 13- 1450

TRANSMITTAL LETTER

Sir:

Transmitted herewith IN THREE COPIES (45 pages total) is an application for extension of patent term of U.S. Patent No. RE38,506 under 35 U.S.C. 156, including an Index of Attachments (Exhibits 1-8). Please charge $1,120.00 in accordance with 37 CFR 1.20(j)(1) to Mintz Levin Cohn Ferris Glovsky and Popeo, Customer No. 35437, Deposit Account No. 50-0311, Reference No. 27499-502 PTE. The undersigned has authority to request that the Office charge this account for any other fees in connection with this application. A duplicate copy of this Transmittal Letter is enclosed herewith.

Respectfully submitted,

Dated: December 1, 2006

Ivor R. Elrifi, Esq., Reg. No.
Mintz Levin Cohn Ferris Glovsky, *et al.*
666 Third Avenue - 24th Floor
New York, New York 10017
Telephone: (212) 935-3000
Telefax: (212) 983-3115

Date of Hand Delivery: December 1, 2006 Attorney Docket No. 24852-502 PTE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	**U.S. Patent No.: RE38,506 E, issued April 20, 2004; Reissue of 5,369,108, issued November 29, 1994**
To:	**Ronald Breslow, Paul A. Marks, Richard A. Rifkind, Branko Jursic**
Assignee:	**Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York**
Title:	**Potent Inducers of Terminal Differentiation and Methods of Use Thereof**

MAIL STOP HATCH-WAXMAN PTE
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Applicants, patent owners Sloan-Kettering Institute for Cancer Research, New York, NY and The Trustees of Columbia University in the City of New York, NY, request extension of the term of U.S. Patent Number RE38,506 E ("the '506 patent"), pursuant to 35 U.S.C. § 156. A copy of the '506 patent (with certificate of correction) is provided as Exhibit 1.

United States Patent No. RE38,506 E, naming Ronald Breslow, Paul A. Marks, Richard A. Rifkind and Branko Jursic as inventors, entitled "Potent Inducers of Terminal

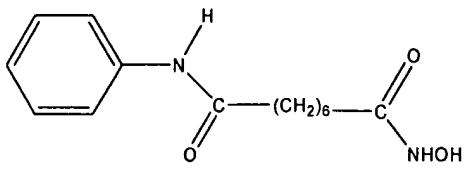
Differentiation and Methods of Use Thereof", was granted on April 20, 2004. U.S. Patent No. RE38,506 E is a reissue patent of U.S. Patent No. 5,369,108, which issued on November 29, 1994. The entire right, title, and interest in the '506 patent was assigned to Sloan-Kettering Institute for Cancer Research and to The Trustees of Columbia University in the City of New York in an assignment recorded in the records of the United States Patent and Trademark Office at Reel/Frame 005935/0910 on 12/9/1991. A copy of the assignment is provided as Exhibit 2.

Merck is the sponsor of New Drug Application ("NDA") No. 21-991 for Zolinza™ (vorinostat, suberoylanilide hydroxamic acid), which is claimed in U.S. Patent No. RE38,506 E. The rights in the '506 patent held by Sloan-Kettering Institute for Cancer Research and by the Trustees of Columbia University in the City of New York were exclusively licensed to Aton Pharma ("Aton"), and are now exclusively licensed to Merck, as a result of Merck's acquisition of Aton. A letter from Merck to Sloan-Kettering Institute for Cancer Research and to the Trustees of Columbia University in the City of New York confirming that the patent owners are authorized to rely on Merck's activities before the FDA in connection with Merck's application under 21 U.S.C. § 355(b) for approval to market Zolinza™ for purposes of this application to extend the term of the '506 patent is attached as Exhibit 3. A Power of Attorney is attached as Exhibit 4 confirming that the undersigned registered practitioner is authorized to act on behalf of Applicants.

Applicants hereby request an extension of patent term under 35 U.S.C. § 156, as provided by 37 C.F.R. § 1.730(c), by providing the following information required under convenience of the Office. The information is presented in a format that follows the paragraph numbering in 37 C.F.R. § 1.740.

(1) Identification of the Approved Product [§ 1.740(a)(1)]

The approved product, Zolinza™ contains an active ingredient, vorinostat, having the chemical name suberoylanilide hydroxamic acid and the molecular structure shown below:



(2) Federal Statute Governing Regulatory Approval of the Approved Product [§ 1.740(a)(2)]

The approved product Zolinza™ was subject to regulatory review under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355).

(3) Date of Approval for Commercial Marketing [§ 1.740(a)(3)]

Merck received permission for commercial marketing or use of Zolinza™ under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) on October 6, 2006. A copy of the letter from the FDA approving marketing of Zolinza™ is attached as Exhibit 5. A copy of the approved label for Zolinza™ is attached as Exhibit 6.

(4) Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [§ 1.740(a)(4)]

The active ingredient in Zolinza™ is vorinostat, which has never been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act prior to the approval of NDA 21-991 by the Food and Drug Administration on October 6, 2006. Zolinza™ was approved under 21 U.S.C. § 355(b) for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

(5) Statement Regarding Timeliness of Submission of Patent Term Extension Request [§ 1.740(a)(5)]

This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The date of the last day on which the application could be submitted being December 6, 2006. The present application, therefore, is timely submitted.

(6) Complete Identification of the Patent for Which Extension Is Being Sought [§ 1.740(a)(6)]

The patent for which extension is being sought is identified as follows:

Inventors: Ronald Breslow
Paul A. Marks
Richard A. Rifkind
Branko Jursic

Patent No.: RE38,506 E, Reissue of Patent No. 5,369,108

Title: Potent Inducers of Terminal Differentiation and Methods of Use Thereof

U.S. 5,369,108 Issued: November 29, 1994

RE38,506 E Issued: April 20, 2004

Expires: November 29, 2011

(7) Copy of the Patent for Which an Extension is Being Sought [§ 1.740(a)(7)]

An extension is being sought for U.S. Patent No. RE38,506 E; a copy (with certificate of correction) is attached as Exhibit 1.

(8) Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [§ 1.740(a)(8)]

A copy of the most recent maintenance fee statement is attached as Exhibit 7. No disclaimer or reexamination certificate has been filed and/or issued for U.S. Patent No. RE38,506 E. A certificate of correction for U.S. Patent No. RE38,506 E issued on August 29, 2006 (copy attached at Exhibit 1).

(9) Statement Regarding Patent Claims Relative to Approved Product [§ 1.740(a)(9)]

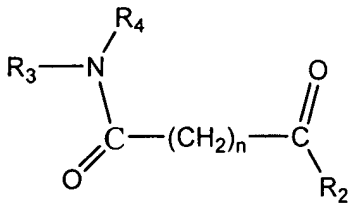
The statements provided herein are made solely to comply with the requirements of 37 C.F.R §1.740(a)(9). We note that, as the M.P.E.P. acknowledges, the requirement of 37 C.F.R. § 1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed; and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicants as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.

(a) At least the following claim of U.S. Patent No. RE38,506 E covers the approved product. Specifically, the approved product is claimed in Claims 2-4 and 16, 18-21 and 24.

(b) Pursuant to M.P.E.P. § 2573 and 37 C.F.R. §1.740(a)(9), the following explanation is provided which shows how each of the above-listed claims of the patent claim the approved product, or a method of making or using the approved product.

Claims 2-4, 16, 18-21 and 24 of U.S. Patent No. RE38,506 E are recited below, along with an explanation which shows how the claim reads on the approved product:

2. A compound of [claim 1] having the structure:



wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino[, hydroxyl, amino, alkylamino, or alkyloxy] group; [and] n is an integer from [about 4] *5* to [about 8] *7*; *and R_3 --N--R_4 and R_2 are different.*

Compound claim 2 reads on the approved product when the variables are defined as follows:

n is 6,

R_2 is hydroxylamino

R_3 and R_4 are different from each other and are a hydrogen atom or aryl.

3. A compound of claim 2, wherein [R_2 is a hydroxylamino, hydroxyl, amino, methylamino, or methoxy group and] n is 6.

Compound claim 3 reads on the approved product when the variables are defined as follows:

R_2 is hydroxylamino

R_3 and R_4 are different from each other and are a hydrogen atom or aryl.

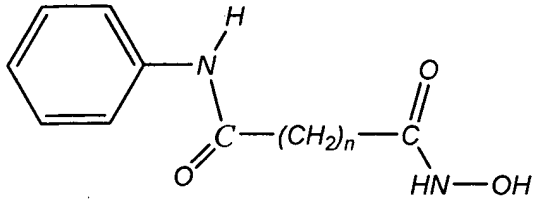
4. A compound of claim 3, wherein R_4 is a hydrogen atom and R_3 is a substituted or unsubstituted phenyl group.

Compound claim 4 reads on the approved product, suberoylanilide hydroxamic acid, where R_3 is an unsubstituted phenyl group.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 2.

Composition claim 16 reads on the approved product, suberoylanilide hydroxamic acid.

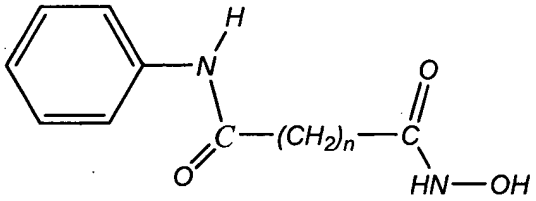
18. *A compound having the structure:*



wherein n is an integer selected from the group consisting of 5, 6, 7 and 8.

Compound claim 18 reads on the approved product, suberoylanilide hydroxamic acid, when n = 6.

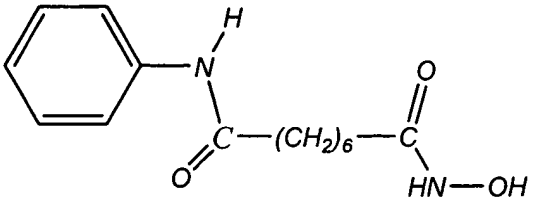
19. *A pharmaceutical composition comprising a therapeutically effective amount of a compound having the structure:*



wherein n is an integer selected from the group consisting of 5, 6, 7 and 8: and a pharmaceutically acceptable carrier.

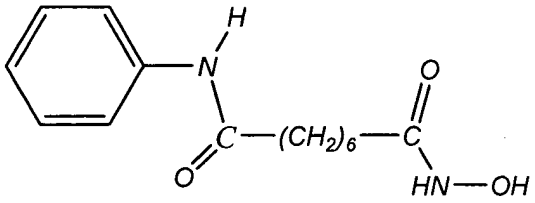
Composition claim 19 reads on the approved product, suberoylanilide hydroxamic acid, when n = 6.

20. *A compound having the structure:*



Compound claim 20 reads on the approved product, suberoylanilide hydroxamic acid.

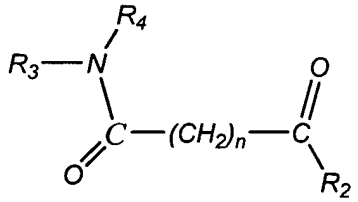
21. *A pharmaceutical composition comprising a therapeutically effective amount of a compound having the structure:*



and a pharmaceutically acceptable carrier.

Composition claim 21 reads on the approved product, suberoylanilide hydroxamic acid.

24. A compound having the structure:



wherein R_3 is hydrogen and R_4 cycloalkyl, aryl, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino group; and n is an integer selected from the group consisting of 5, 6, 7, and 8.

Compound claim 24 reads on the approved product when the variables are defined as follows:

n is 6 and

R_4 is aryl.

In addition, at least claims 2-4 and 16 of U.S. Patent No. 5,369,108 (upon which U.S. Patent No. RE38,506 E is based), as issued on November 29, 1994, covered the approved product.

(10) Relevant Dates Under 35 U.S.C. § 156 for Determination of Applicable Regulatory Review Period [§1.740(a)(10)]

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable review period are as follows:

(a) Patent Issue Date

U.S. Patent No. RE38,506 E which is a reissue of Patent No. 5,369,108, issued on April 20, 2004. U.S. Patent No. 5,369,108 issued on November 29, 1994. (Exhibit 1)

(b) IND Effective Date [35 U.S.C. §156(a)(1)(B)(i); 37 C.F.R §1.740(a)(10)(i)(A)]

Investigational New Drug Application (IND 58,915) was submitted on September 2, 1999 and the IND was effective on October 2, 1999. (See Exhibit 8)

(c) NDA Submission Date [35 U.S.C. § 156(g)(1)(B)(i); 37 C.F.R. § 1.740(a)(10)(i)(B)]

New Drug Application (NDA 21-991) was submitted on December 6, 2005. (See Exhibit 8)

(d) NDA Issue Date [35 U.S.C. § 156(g)(1)(B)(ii); 37 C.F.R. §I.740(a)(10)(i)(C)]

New Drug Application (NDA 21-991) was approved on October 6, 2006. (Exhibit 5)

(11) Summary of Significant Events During Regulatory Review Period [§ 1.740(a)(11)]

A brief description of the significant activities undertaken during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached as Exhibit 8. The owners of the patent, Sloan-Kettering Institute for Cancer Research and the Trustees of Columbia University in the City of New York, are authorized to rely on Merck's activities for the purpose of the present application under 35 U.S.C. § 156, as evidenced by the letter attached as Exhibit 3. *See* M.P.E.P. § 2752.

(12) Statement Concerning Eligibility for and Duration of Extension Sought Under § 156 [§ 1.740(a)(12)]

(12)(A) Applicants are of the opinion that U.S. Patent No. RE38,506 E is eligible for an extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

a) 35 U.S.C. § 156(a): U.S. Patent No. RE38,506 E claims a product.

b) 35 U.S.C. § 156(a)(l): The term of U.S. Patent No. RE38,506 E has not expired before submission of this application.

c) 35 U.S.C. § 156(a)(2): The term of U.S. Patent No. RE38,506 E has never been extended under this provision of the law.

d) 35 U.S.C. § 156(a)(3): The application is submitted by an agent of the patent owner of record in accordance with the requirements of 35 U.S.C. § 156(d) and the rules of the U.S. Patent and Trademark Office.

e) 35 U.S.C. § 156(a)(4): The product Zolinza™ has been subjected to a regulatory review period before its commercial marketing or use.

f) 35 U.S.C. § 156(a)(5)(A): The commercial marketing or use of Zolinza™ after the regulatory review period is the first permitted commercial marketing or use of product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) under which such regulatory review period occurred.

g) 35 U.S.C. § 156(c)(4): No other patent has been extended for the same regulatory review period for the product, Zolinza™.

(12)(B) The length of extension of the patent term of U.S. Patent No. RE38,506 E claimed by Applicants is 1433 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on October 2, 1999 and ended on October 6, 2006 which is a total of 2562 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) began on October 2, 1999 and ended on December 6, 2005, which is 2258 days; and

(ii) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) began on December 6, 2005 and ended on October 6, 2006, which is 304 days;

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(B)(a) above (2562 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the U.S. Patent No. 5,369,108 issued is 0 days, and,

(ii) The number of days during which Applicants did not act with due diligence which is 0 days, and

(iii) One-half of (2258 days), which is 1129 days;

(iv) The regulatory review period is calculated by subtracting the number of days determined in subparagraph 12(B)(b)(i)-(iii) from the entire regulatory review period, as determined in subparagraph 12(B)(a) (which is 2562 minus 1129 days) which equals 1433 days.

(c) The number of days as determined in sub-paragraph 12(B)(b)(iv) (1433 days) when added to the term of the patent (November 29, 2011) would result in the date November 1, 2015;

(d) Fourteen years, when added to the date of NDA approval (October 6, 2006) would result in the date October 6, 2020.

(e) The earlier date as determined in subparagraphs 12(B)(c) and 12(B)(d) is November 1, 2015.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five years. Five years when added to the expiration date of the patent (November 29, 2011) would result in the date November 29, 2016.

(g) The earlier date as determined in subparagraph 12(B)(e) and 12(B)(f) is November 1, 2015 which is 1433 days extension from the expiration date of the patent.

(13) Statement Pursuant to 37 C.F.R. [§ 1.740(a)(13)]

Applicants acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. § 1.765.

(14) Applicable Fee [§ 1.740(a)(14)]

The prescribed fee for receiving and acting upon this application is to be charged to Deposit Account 50-0311 as authorized in the attached letter, which is submitted in triplicate.

(15) Name and Address for Correspondence [§ 1.740(a)(15)]

Correspondence related to this application for extension of the patent term of U.S. Patent No. RE38,506 E should be addressed to:

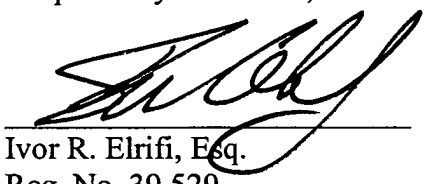
Ivor R. Elrifi, Esq.
Reg. No. 39,529
Mintz Levin Cohn Ferris Glovsky and Popeo PC
666 Third Avenue - 24th Floor
New York, New York 10017
Telephone: (212) 935-3000
Telefax: (212) 983-3115

(16) Additional Copies of the Application for Extension [§ 1.740(a)(16)]

This application for extension of the patent term of U.S. Patent No. RE38,506 E is being submitted as ONE original and TWO additional copies thereof. Applicants hereby certify that the copies submitted herein are true copies.

Transmitted herewith IN THREE COPIES total is the application for extension of patent term of U.S. Patent No. RE38,506 E under 35 U.S.C. § 156. Please charge $1,120.00 in accordance with 37 C.F.R. § 1.20(j)(1) to Mintz Levin Cohn Ferris Glovsky and Popeo, Deposit Account No. 50-0311. The undersigned has authority to request that the Office charge this account for this application.

Respectfully submitted,



Ivor R. Elrifi, Esq.
Reg. No. 39,529
Mintz Levin Cohn Ferris Glovsky
and Popeo PC
666 Third Avenue - 24th Floor
New York, New York 10017
Telephone: (212) 935-3000
Telefax: (212) 983-3115

Index of Attachments.

Exhibit 1: Copy of U.S. Patent No. RE38,506 E, with Certificate of Correction

Exhibit 2: Copy of Assignment from inventors to Sloan-Kettering Institute for Cancer Research; Copy of Assignment from inventors to the Trustees of Columbia University in the City of New York

Exhibit 3: Letter from Merck to Sloan-Kettering Institute for Cancer Research and to the Trustees of Columbia University in the City of New York authorizing Sloan-Kettering Institute for Cancer Research and the Trustees of Columbia University in the City of New York to rely on Merck's regulatory activities

Exhibit 4: Authorization of Agent/Power of Attorney for U.S. Patent No. RE38,506 E

Exhibit 5: Copy of Letter from the FDA approving marketing of Zolinza™

Exhibit 6: Copy of Approved label for Zolinza™

Exhibit 7: Maintenance Fee Statement for U.S. Patent No. RE38,506 E

Exhibit 8: Brief Description of Significant Activities During Applicable Regulatory Review

TRA 2224934v.1

US00RE38506E

(19) **United States**

(12) **Reissued Patent**

Breslow et al.

(10) **Patent Number: US RE38,506 E**

(45) **Date of Reissued Patent: Apr. 20, 2004**

(54) **POTENT INDUCERS OF TERMINAL DIFFERENTIATION AND METHODS OF USE THEREOF**

(75) Inventors: **Ronald Breslow**, Englewood, NJ (US); **Paul A. Marks**, Bridgewater, CT (US); **Richard A. Rifkind**, New York, NY (US); **Branko Jursic**, New Orleans, LA (US)

(73) Assignees: **Sloan-Kettering Institute for Cancer Research**, New York, NY (US); **The Trustees of Columbia University in the City of New York**, New York, NY (US)

(21) Appl. No.: **10/004,411**

(22) Filed: **Nov. 2, 2001**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,369,108**
Issued: **Nov. 29, 1994**
Appl. No.: **07/771,760**
Filed: **Oct. 4, 1991**

(51) **Int. Cl.**[7] **A01N 43/40**; A01N 43/78; C07D 211/32; C07C 235/00; C07C 237/00

(52) **U.S. Cl.** **514/316**; 514/330; 514/352; 514/371; 514/616; 546/187; 546/189; 546/262; 564/152; 564/155; 564/158; 564/160; 564/161; 564/169; 564/170; 564/171; 564/182; 564/188; 564/192; 564/193; 564/194; 564/197; 564/199; 564/200; 564/201; 564/202; 564/204; 564/209

(58) **Field of Search** 514/371, 316, 514/330, 616, 352; 564/152, 155, 158, 160, 161, 169, 170, 171, 182, 188, 192, 193, 194, 197, 199, 200, 201, 202, 204, 209; 546/187, 189, 262

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,279,560	A	4/1942	Dietrich	252/47
2,279,973	A	4/1942	Dietrich	252/51
2,346,665	A	4/1944	Cupery	260/509
2,895,991	A	7/1959	Randall et al.	260/558
3,450,673	A	6/1969	McKillip	260/75
3,632,783	A	1/1972	Stonis	424/320
3,875,301	A	4/1975	Windheuser	424/45
4,056,524	A	11/1977	Walker	260/239
4,442,305	A	4/1984	Weitl et al.	562/451
4,480,125	A	10/1984	Haas et al.	564/144
4,537,781	A	8/1985	Darling	514/616
4,611,053	A	9/1986	Sasa	528/335
4,614,815	A	9/1986	Cognigni et al.	560/88
4,663,353	A	5/1987	Bistline, Jr. et al.	514/617
4,801,748	A	1/1989	Murahashi et al.	564/126
4,863,967	A	9/1989	Hall et al.	514/615
4,882,346	A	11/1989	Driscoll et al.	514/389
5,055,608	A	10/1991	Marks et al.	560/169
5,098,598	A	3/1992	Sankey et al.	252/186.42
5,175,191	A	12/1992	Marks et al.	514/575
5,189,179	A	2/1993	McDonald et al.	548/495
5,330,744	A	7/1994	Pontremoli et al.	424/10
5,366,982	A	11/1994	Dereu et al.	514/340

FOREIGN PATENT DOCUMENTS

CH	421 933	4/1967
DE	35 05 250	9/1985
EP	0 119428	9/1984
EP	0 433662	6/1991
EP	0 478 954	4/1992
EP	0 576941	1/1994
GB	2 225 012	5/1990
WO	WO 91/00257	1/1991
WO	WO 91/08191	6/1991

OTHER PUBLICATIONS

Endres, G.F. and J. Epstein, "Synthesis of Some Hydroxamic Acids. Reactivity with Isopropyl Methylphosphonofluoridate (GB)", *J. Org. Chem.*, 24: 1497–1501 (1959).

Abstract for Accession No. 1966–26456F/196800 from, World Patent Index Database.

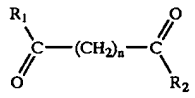
Hozumi, et al., "Induction of Erythroid Differentiation in Murine Erythroleukemia Cells by N–Substituted Polymethylene Diamides," *Int. J. Cancer*, 23:119–122 (1979).

(List continued on next page.)

Primary Examiner—Alan L. Rotman
Assistant Examiner—Raymond Covington
(74) *Attorney, Agent, or Firm*—Hamilton, Brook, Smith & Reynolds, P.C.

(57) **ABSTRACT**

The present invention provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different from each other; when R_1 and R_2 are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiozoleamino group; when R_1 and R_2 are different, R_1=R_3—N—R_4, wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group and R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and n is an integer from about 4 to about 8.

The present invention also provides a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells. Moreover, the present invention provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells. Lastly, the present invention provides a pharmaceutical composition and a therapeutically acceptable amount of the compound above.

23 Claims, No Drawings

OTHER PUBLICATIONS

Marks, P.A., et al., "Polar/apolar Chemical Inducers of Differentiation of Transformed Cells: Strategies to Improve Therapeutic Potential," *Proc. Natl. Acad. Sci.*, 86:6358–6362 (1989).

Chun, J.G., et al., "Hexamethylene Bisacetamide: A Polar–Planar Compound Entering Clinical Trials as a Differentiating Agent," *Cancer Treatment Reports*, 70(8): 991–996 (1986).

Reuben, R.C., et al., "Inducers of Erythroleukemic Differentiation," J. Biolog. Chem., 253:4214–4218 (1978).

Tanaka, M., et al., "Induction of Erythroid Differentiation in Murine Virus Infected Erythroleukemia Cells By Highly Polar Compounds," Proc. Natl. Acad. Sci., 72(3):1003–1006 (1975).

Fibach, E., et al., "Effect of Hexamethylene Bisacetamide on the Commitment to Differentiation of Murine Erythroleukemia Cells," Cancer Research, 37:440–444 (1977).

Melloni, E., et al., "Vincristine–resistant Erythroleukemia Cell Line Has Markedly Increased Sensitivity to Hexamethylenebisacetamide–Induced Differentiation." Chem. Abs., 1988, 109, Abstract No. 47737e. (From Proc. Natl. Acad. Sci. USA, 85(11):3835–3839, 1988).

Haces, A., et al., "Chemical Differentiating Agents. Differentiation of HL–60 Cells by Hexamethylenebis[acetamind] Angalogues," J. Med. Chem., 30:405–409 (1987).

Das, M.K., et al., "Synthesis of Some Dihydroxamic Acid Siderophores", Chem. Abs., 1984, 101, Abstract No. 54665t. (From J. Chem Eng. Data, 1984, 29(3):345–348, 1984.

Brown, D.A., et al., "A Facile Synthesis of Aliphatic Dihydroxamic Acids of General Formula RONR1–CO–(CH2)n–CO–NR1OR," Chem. Abs., 1986, 105, Abstract No. 78501v. (From Synth. Commun., 15(13):1159–1164, 1985).

Hynes, J.B., "Hydroxylamine Derivatives as Potential Antimalarial Agents. 1. Hydroxamic Acids1." J. Med. Chem., 13(6):1235–1237 (1970).

Tabernero, E., et al., "Antitrypanosomal (T. Venezuelense) and Antimycotic Effect of Various Hydroxamic Acids," Chem. Abs., 1983, 98, Abstract No. 191329v. (From Acta. Cient. Venez., 32(5):411–416, 1981).

Morrison, R. T., and Boyd, R.N., "Conversion of Amines Into Substituted Amides." In Organic Chemistry (3rd ed.), Allyn and Bacon, Inc., Boston, p. 755 (1973).

Weitl, F.L., and Raymond, K.N., "Lipophilic Enterobactin Analogues Terminally N–Alkylated Spermine/Spermidine Catecholcarboxamides," *J. Org. Chem.*, 46:5234–5237 (1981).

Paolini, J.P., et al., "N^4,$N^{4'}$–Decamethylenebis–4–aminopyridine and N^9,$N^{9'}$–Decamethylenebis–9–aminoacridine," J. Med. Chem., 12(4):701 (1969).

Cleaver, C.S., and Pratt, B.C., "Synthesis of 2,2'–Bis–[5(4H)–oxazolones]," J. Amer. Chem. Soc., 77:1544 (1955).

Breslow, R., et al., "Potent Cytodifferentiating Agents Related to Hexamethylenebisacetamide," Proc. Natl. Acad. Sci. USA, 88:5542–5546 (1991).

Brown, D.A., "Design of Metal Chelates With Biological Activity. 5. Complexation Behavior of Dihydroxamic Acids with Metal Ions," American Chemical Society, 3729–3796 (1986).

Chugai Pharmaceutical Co., Ltd., "Benzenehydroxycarboxamides as Fumigant Insecticide Base Materials." (From 5–Agrochemicals, 1984, 101, Abstract No. 124925d).

Mueller, G., et al., "Coordination Chemistry of Microbial Iron Transport Compounds. 31. The Mechanism and Specificity of Iron Transport in *Rhodotorula Pilimanae* Probed by Synthetic Analogs of Rhodotorulic Acid." (From Chem. Abs., 1985, 103, Abstract No. 192908s.

Prabhakar, Y.S., et al., "Quantitative Correlations of Biological Activities of Dactinomycin Analogs and Methotrexate Derivatives with Van Der Waals Volume," *Birla Institute of Technology and Science*, Pilani (India), pp. 1030–1033.

Linfield, W.M., et al., "Antibacterially Active Substituted Anilides of Carboxylic and Sulfonic Acids," J. Med. Chem., 26:1741–1746 (1983).

Devlin, J.P., et al., "Studies Concerning the Antibiotic Actinonin. Part VI. Synthesis of Structural Analogues of Actinonin by Dicyclohexylcarbodi–imide Coupling Reactions," J. Chem. Soc. Perkins Trans. 1(9):848–851 (1975).

Hirom, P.C., et al., "Bile and Urine as Complementary Pathways for the Excretion of Foreign Organic Compounds," Xenobiotica, 6(1):55–64 (1976).

Hirom, P.C., et al., "Molecular Weight and Chemical Structure as Factors in the Biliary Excretion of Sulphonamides in the Rat," Xenobiotica, 2(3):205–214 (1972).

Hill, J.W., and Carothers, W.H., "Studies of Polymerization and Ring Formation. XIX. Many–Membered Cyclic Anhydrides," J. Am. Chem. Soc., 55:5023–5031 (1933).

Lion, C., et al., "Synthese Dans La Chimie Des Phenanthridines. II. Preparation D'Une Nouvelle Serie D'ω–(Phenanthridinyl–6) Alcanoates De Methyle Ou D'Ethyle," Bull. Soc. Chim. Belg., 98(8):567–573 (1989).

Lion, C., et al., "Synthese Dans La Chimie Des Phenanthridines. III. Preparation De Quelques Modeles D'Acides ω–(Diamino –3,8 Phenanthridinyl–6) Carboxyliques," *Bull. Soc. Chim. Belg.*, 99(3):171–181 (1990).

Wojcik, A., and, Adkins, H., "Catalytic Hydrogenation of Amides to Amines," J. Amer. Chem. Soc., 56:2419 (1932).

Abstract for Accession No. 1984–214010/198435 from, World Patent Index Database.

Abstract for Accession No. 1985–231331/198538 from Derwent Info Ltd.

POTENT INDUCERS OF TERMINAL DIFFERENTIATION AND METHODS OF USE THEREOF

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

BACKGROUND OF THE INVENTION

Throughout this application various publications are referenced by arabic numerals within parentheses. Full citations for these publications may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

Cancer is a disorder in which a population of cells has become, in varying degrees, unresponsive to the control mechanisms which normally govern proliferation and differentiation. For many years there have been two principal strategies for chemotherapeutic treatment of cancer: a) blocking hormone-dependent tumor cell proliferation by interference with the production of peripheral action of sex hormones; and b) killing cancer cells directly by exposing them to cytotoxic substances, which injure both neoplastic and normal cell populations.

Relatively recently, cancer therapy is also being attempted by the induction of terminal differentiation of the neoplastic cells (1). In cell culture models differentiation has been reported by exposure of cells to a variety of stimuli, including: cyclic AMP and retinoic acid (2,3), aclarubicin and other anthracyclines (4).

There is abundant evidence that neoplastic transformation does not necessarily destroy the potential of cancer cells to differentiate (1,5,6). There are many examples of tumor cells which do not respond to the normal regulators of proliferation and appear to be blocked in the expression of their differentiation program, and yet can be induced to differentiate and cease replicating. A variety of agents, including some relatively simple polar compounds (5,7–9), derivatives of vitamin D and retinoic acid (10–12), steroid hormones (13), growth factors (6,14), proteases (15,16), tumor promoters (17,18), and inhibitors of DNA or RNA synthesis (4,19–24), can induce various transformed cell lines and primary human tumor explants to express more differentiated characteristics.

Early studies by the present inventors identified a series of polar compounds that were effective inducers of differentiation in a number of transformed cell lines (8,9). Of these, the most effective inducer, was the hybrid polar/apolar compound N,N'-hexamethylene bisacetamide (HMBA) (9). The use of this polar/apolar compound to induce murine erythroleukemia cells (MELC) to undergo erythroid differentiation with suppression of oncogenicity has provided a useful model to study inducer-mediated differentiation of transformed cells (5,7–9). HMBA-induced MELC terminal erythroid differentiation is a multistep process. Upon addition of HMBA to MELC (745A-DS19) in culture, there is a latent period of 10 to 12 hours before commitment to terminal differentiation is detected. Commitment is defined as the capacity of cells to express terminal differentiation despite removal of inducer (25). Upon continued exposure to HMBA there is progressive recruitment of cells to differentiate. The present inventors have reported that MELC

cell lines made resistant to relatively low levels of vincristine become markedly more sensitive to the inducing action of HMBA and can be induced to differentiate with little or no latent period (26).

HMBA is capable of inducing phenotypic changes consistent with differentiation in a broad variety of cells lines (5). The characteristics of the drug induced effect have been most extensively studied in the murine erythroleukemia cell system (MELC) (5,25,27,28). MELC induction of differentiation is both time and concentration dependent. The minimum concentration required to demonstrate an effect in vitro in most strains is 2 to 3 mM; the minimum duration of continuous exposure generally required to induce differentiation in a substantial portion (>20%) of the population without continuing drug exposure is about 36 hours.

The primary target of action of HMBA is not known. There is evidence that protein kinase C is involved in the pathway of inducer-mediated differentiation (29). The in vitro studies provided a basis for evaluating the potential of HMBA as a cytodifferentiation agent in the treatment of human cancers (30). Several phase I clinical trials with HMBA have been completed (31–36). Clinical trials have shown that this compound can induce a therapeutic response in patients with cancer (35,36). However, these phase I clinical trials also have demonstrated that the potential efficacy of HMBA is limited, in part, by dose-related toxicity which prevents achieving optimal blood levels and by the need for intravenous administration of large quantities of the agent, over prolonged periods.

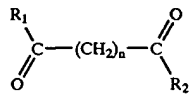
Recently, the present inventors have reported a number of compounds related to HMBA with polar groups separated by apolar linkages that, on a molar basis, are as active (37) or 100 times more active than HMBA (38). As a class, however, it has been found that the symmetrical dimers such as HMBA and related compounds are not the best cytodifferentiating agents.

It has unexpectedly been found that the best compounds comprise two polar end groups separated by a flexible chain of methylene groups, wherein one or both of the polar end groups is a large hydrophobic group. Preferably, the polar end groups are different and only one is a large hydrophobic group. These compounds are unexpectedly a thousand time more active than HMBA and ten times more active than HMBA related compounds.

This new class of compounds of the present invention may be useful for selectively inducing terminal differentiation of neoplastic cells and therefore aid in treatment of tumors in patients.

SUMMARY OF THE INVENTION

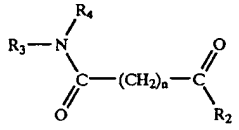
The present invention provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different from each other; when R_1 and R_2 are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiozoleamino group; when R_1 and R_2 are different, R_1=R_3—N—R_4, wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or

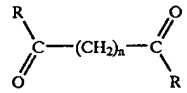
unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group and R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and n is an integer from about 4 to about 8.

The present invention also provides the compound above having the structure:



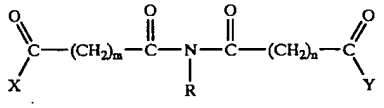
wherein each of R_3 and R_4 are independently the same as or different from each other are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and n is an integer from about 4 to about 8.

The present invention also provides the compound above having the structure:



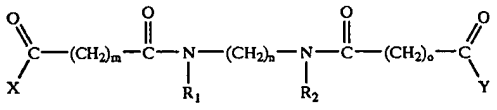
wherein R is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiozoleamino group; and n is an integer from about 4 to about 8.

The present invention also provides the compound having the structure:



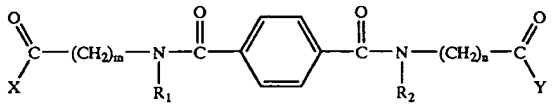
wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; R is a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention further provides the compound having the structure:



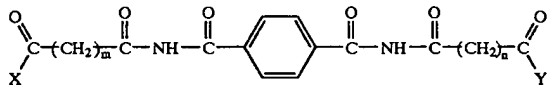
wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m, n, and o are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention still further provides the compound having the structure:



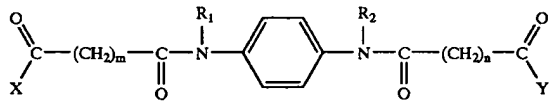
wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to 8.

The present invention also provides the compound having the structure:



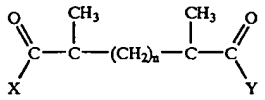
wherein each of X and Y are independently, the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention also provides the compound having the structure



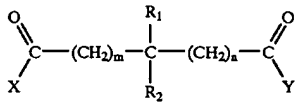
wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to 8.

The present invention further provides the compound having the structure:



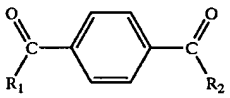
wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and n is an integer from about 0 to about 8.

The present invention still further provides the compound having the structure:



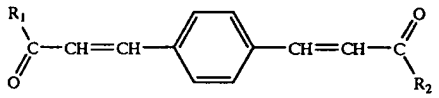
wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, aryloxy, carbonylhydroxylamino, or fluoro group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention also provides the compound having the structure:



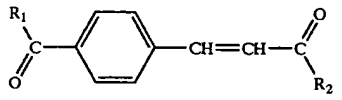
wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

The present invention also provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different form each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

The present invention further provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

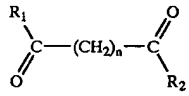
In addition, the present invention provides a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells which comprises contacting the cells under suitable conditions with an effective amount of any of the compounds above, effective to selectively induce terminal differentiation.

The present invention also provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells which comprises administering to the patient an effective amount of any of the compounds above, effective to selectively induce terminal differentiation of such neoplastic cells and thereby inhibit their proliferation.

Lastly, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically acceptable amount of any of the compounds above.

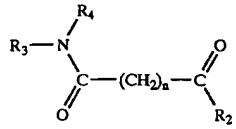
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different from each other; when R_1 and R_2 are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiozoleamino group; when R_1 and R_2 are different, R_1=R_3—N—R_4, wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridino group, or R_3 and R_4 bond together to form a piperidine group and R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and n is an integer from about 4 to about 8.

The present invention also provides the compound above having the structure:



wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond

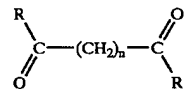
together to form a piperidine group; R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and n is an integer from about 4 to about 8.

In the preferred embodiment of the compound above, R_2 is a hydroxylamino, hydroxyl, amino, methylamino, dimethylamino, or methoxy group and n is 6. Most preferably, R_4 is a hydrogen atom and R_3 is a substituted or unsubstituted phenyl group.

The phenyl group may be substituted with a methyl, cyano, nitro, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methyoxy, benzyloxy, phenylaminooxy, phenylmethoxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

In other preferred embodiments of the compound above, R_4 is a hydrogen atom and R_3 is a cyclohexyl group; R_4 is a hydrogen atom and R_3 is a methyoxy group; R_3 and R_4 each bond together to form a piperidine group; R_4 is a hydrogen atom and R_3 is a hydroxyl group; R_4 is a hydrogen atom and R_3 is a benzyloxy group; R_4 is a hydrogen atom and R_3 is a δ-pyridine group; R_4 is a hydrogen atom and R_3 is a β-pyridine group; R_4 is a hydrogen atom and R_3 is a α-pyridine group; R_3 and R_4 are both methyl groups; or R_4 is a methyl group and R_3 is a phenyl group.

The present invention also provides the compound having the structure:

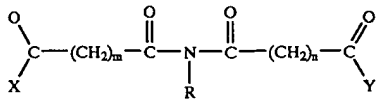


wherein R is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiozoleamino group; and n is an integer from about 4 to about 8.

In the preferred embodiment of the compound above, R is a substituted or unsubstituted phenylamino group. The phenylamino group may be substituted with a cyano, methylcyano, nitro, carboxyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, trifluoromethyl, hydroxylaminocarbonyl, N-hydroxylaminocarbonyl, methoxycarbonyl, chloro, fluoro, methyl, methoxy, 2,3-difluoro, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 2,6-difluoro, 3,5-difluoro, 2,6-difluoro, 2,3,6-trifluoro, 1,2,3-trifluoro, 3,4,5-trifluoro, 2,3, 4,5-tetrafluoro, or 2,3,4,5,6-pentafluoro group.

In another embodiment of the compound above, R is a cyclohexylamino group.

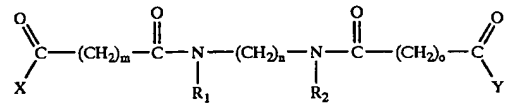
The present invention also provides the compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; R is a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy-group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In the preferred embodiment of the compound above, each of X, Y, and R is a hydroxyl group and each of m and n is 5.

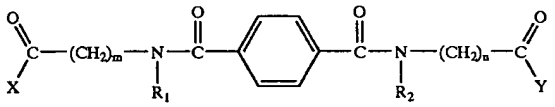
The present invention also provides the compound having the structure:



wherein each of X and Y are independently the same as or different form each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m, n, and o are independently the same as or different from each other and are each an integer from about 0 to about 8.

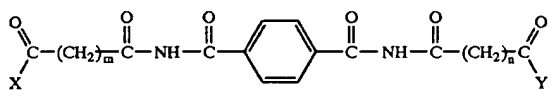
In the preferred embodiment of the compound above, each of X and Y is a hydroxyl group and each of R_1 and R_2 is a methyl group. Most preferably, each of n and o is 6, and m is 2.

The present invention also provides the compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention also provides the compound having the structure:

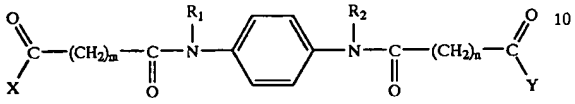


wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino,

alkyloxyalkylamino, or aryloxyalkylamino group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

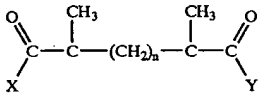
In the preferred embodiment of the compound above, each of X and Y is a hydroxyl group and each of m and n is 5.

The present invention also provides the compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

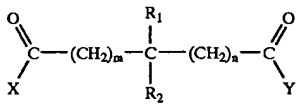
The present invention also provides the compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and n is an integer from about 0 to about 8.

In the preferred embodiment of the compound above, each of X and Y is a dimethylamino group and n is 4 or 5.

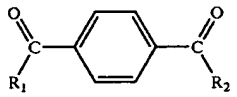
The present invention also provides the compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, aryloxy, carbonylhydroxylamino, or fluoro group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In the preferred embodiment of the compound above, each of X and Y is a hydroxylamino group, R_1 is a methyl group, R_2 is a hydrogen atom, and each of m and n is 2. In another preferred embodiment, each of X and Y is a hydroxylamino group, R_1 is a carbonylhydroxylamino group, R_2 is a hydrogen atom, and each of m and n is 5. In a further preferred embodiment, each of X and Y is a hydroxylamino group, each of R_1 and R_2 is a fluoro group, and each of m and n is 2.

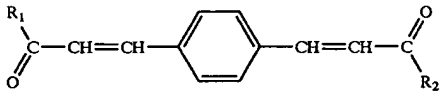
The present invention also provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

Preferably, R_1 is a phenylamino group and R_2 is a hydroxylamino group.

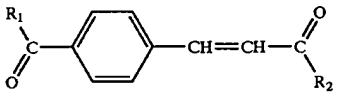
The present invention also provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

Preferably, R_1 is phenylamino group and R_2 is hydroxylamino group.

The present invention also provides the compound having the structure:



wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

In the preferred embodiment, either R_1 or R_2 is a hydroxylamino group.

The present invention also provides a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells which comprises contacting the cells under suitable conditions with an effective amount of any of the compounds above, effective to selectively induce terminal differentiation.

The contacting must be performed continuously for a prolonged period of time, i.e. for at least 48 hours, preferably for about 4–5 days or longer.

The method may be practiced in vivo or in vitro. If the method is practiced in vitro, contacting may be effected by incubating the cells with the compound. The concentration of the compound in contact with the cells should be from about 1 μM to about 25 mM, preferably from 4 μM to about 5 mM. The concentration depends upon the individual compound and the state of the neoplastic cells.

The method may also comprise initially treating the cells with an antitumor agent so as to render them resistant to an antitumor agent and subsequently contacting the resulting resistant cells under suitable conditions with an effective amount of any of the compounds above, effective to selectively induce terminal differentiation of such cells.

The antitumor agent may be one of numerous chemotherapy agents such as an alkylating agent, an antimetabolite, a hormonal agent, an antibiotic, colchicine, a vinca alkaloid, L-asparaginase, procarbazine, hydroxyurea, mitotane, nitrosoureas or an imidazole carboxamide. Suitable agents are those agents which promote depolarization of tubulin. Preferably the antitumor agent is colchicine or a vinca alkaloid; especially preferred are vinblastine and vincristine. In embodiments where the antitumor agent is vincristine, the cells preferably are treated so that they are resistant to vincristine at a concentration of about 5 mg/ml. The treating of the cells to render them resistant to an antitumor agent may be effected by contacting the cells with the agent for a period of at least 3–5 days. The contacting of the resulting cells with any of the compounds above is performed as described previously.

The present invention also provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells which comprises administering to the patient an effective amount of any of the compounds above, effective to selectively induce terminal differentiation of such neoplastic cells and thereby inhibit their proliferation.

The method of the present invention is intended for the treatment of human patients with tumors. However, it is also likely that the method would be effective in the treatment of tumors in other mammals. The term tumor is intended to include any cancer caused by the proliferation of neoplastic cells, such as lung cancer, acute lymphoid myeloma, bladder melanoma, renal carcinoma, breast carcinoma, or colorectal carcinoma. The administration of the compound to the patient may be effected orally or parenterally. To date administration intravenously has proven to be effective. The administration of the compound must be performed continuously for a prolonged period of time, such as for at least 3 days and preferably more than 5 days. In the most preferred embodiments, the administration is effected continuously for at least 10 days and is repeated at intervals wherein at each interval the administration is continuously effected for at least 10 days. For example, the administration may be effected at intervals as short as 5–10 days, up to about 25–35 days and continuously for at least 10 days during each such interval. The optimal interval period will vary depending on the type of patient and tumor. For example, in the incidence of acute leukemia, the so called myelodysplastic syndrome, continuous infusion would seem to be indicated so long as the patient tolerated the drug without toxicity and there was a positive response.

The amount of the compound administered to the patient is less than an amount which would cause toxicity in the patient. In the certain embodiments, the amount of the compound which is administered to the patient is less than the amount which causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. Preferably, the concentration of the compound in the patient's plasma is maintained at about 1.0 mM. It has been found with HMBA that administration of the compound in an amount from about 5 gm/m^2/day to about 30 gm/m^2/day, particularly about 20 gm/m^2/day, is effective without producing toxicity in the patient. The optimal amount of the compound which should be administered to the patient in the practice of the present invention will depend on the particular compound used and the type of cancer being treated.

This invention, in addition to the above listed compounds, is intended to encompass the use of homologs and analogs of such compounds. In this context, homologs are molecules having substantial structural similarities to the above-descried compounds and analogs are molecules having substantial biological similarities regardless of structural similarities.

The method may also comprise initially administering to the patient an amount of an antitumor agent to render the cells resistant to an antitumor agent and subsequently administering to the patient an effective amount of any of the compounds above, effective to selectively induce terminal differentiation of such neoplastic cells and thereby inhibit their proliferation.

The antitumor agent may be one of numerous chemotherapy agents such as an alkylating agent, an antimetabolite, a hormonal agent, an antibiotic, colchicine, a vinca alkaloid, L-asparaginase, procarbazine, hydroxyurea, mitotane, nitrosoureas of an imidazole carboxamide. Suitable agents are those agents which promote depolarization of tubulin. Preferably the antitumor agent is colchicine or a vinca alkaloid; especially preferred are vinblastine and vincristine. In embodiments where the antitumor agent is vincristine, an amount is administered to render the cells are resistant to vincristine at a concentration of bout 5 mg/ml. The administration of the agent is performed essentially as described above for the administration of any of the compounds. Preferably, the administration of the agent is for a period of at least 3–5 days. The administration of any of the compounds above is performed as descried previously.

The present invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier, such as sterile pyrogen-free water, and a therapeutically acceptable amount of any of the compounds above. Preferably, the effective amount is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.

Lastly, the present invention provides the pharmaceutical composition above in combination with an antitumor agent. The antitumor agent may be any of the agents previously described.

The invention is illustrated in the Experimental Details section which follows. This section is set forth to aid in an understanding of the invention but is not intended to, and should not be construed to, limit in any way the invention as set forth in the claims, which follow thereafter.

Experimental Details

Cells and Materials

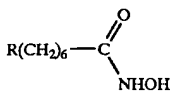
MELC 745A-DS19 cells and the variants of MELC derived from this cell line, namely, the vincristine-resistant MELC V3.17 and VCR.C(2)15 cell lines (26), and the dimethylsulfoxide-resistant cell line, DR10 (39), were maintained in alpha minimal essential medium containing 10% fetal calf serum (16). Cell cultures for all experiments were initiated with cells in logarithmic growth phase (day 2 cultured cells) at a density of 10^5 cells/ml. Inducer compounds were added in the final concentrations indicated below, dissolved in culture medium without fetal calf serum unless otherwise indicated. Cell density and benzidine reactively were determined as described (16).

Commitment to terminal differentiation, characterized by limited cell division (colony size<32 cells) and accumula-

tion of hemoglobin (benzidine reactive colonies) was assayed by a colony cloning assay using 2% methylcellulose as described (25) (see Table 1 for results). HL-60 human leukemia cells, derived from peripheral blood leukocytes of a patient with acute promyelocytic leukemia (40). Induced differentiation of HL-60 cells assayed by determining the proportion of cells that developed the capacity to reduce nitroblue tetrazolium (NBT) (41) (see Table 2 for results).

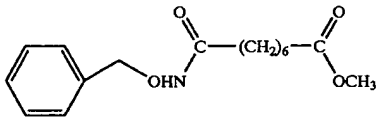
Chemistry

The compounds having the structure:

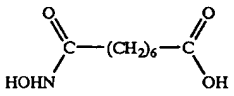


Preparation of $PhCH_2ONHOC(CH_2)_6COOCH_3$:

A solution of suberic acid monomethyl ester (1.9 g; 0.01 mol), oxaloyl chloride (1.75 mL; 2.54 g; 0.02 mol) and 0.1 mL DMF in benzene (200 mL) was stirred overnight at room temperature. The solvent was evaporated and oily residue was dissolved in chloroform (~20 mL) and mixed together with chloroform solution (100 mL) of O-benzylhydroxylamine (2.46 g; 0.02 mol) and pyridine (1.6 mL; 1.68 g; 0.02 mol). The reaction mixture was stirred at room temperature overnight. The chloroform solution was washed with water (50 mL), 10% hydrochloric acid, and again with water (2×50 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was slurried in hexanes (~100 mL) and filtered. The yield of $PhCH_2ONHOC(CH_2)_6COOCH_3$ was 2.61 g (89%).

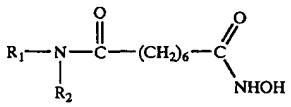


The above suberic acid monobenzyloxyamide monomethyl ester (1 g; 3.4 mol) was dissolved in dry methanol (50 mL) and 5% Pd-C (50 mg) was added. The black suspension was shaken under hydrogen pressure (~50 psi) overnight at room temperature. The catalyst was separated by filtration, and filtrate was evaporated. The solid residue was slurried in hexanes (~20 mL) and filtered. The yield of the monomethyl ester monohydroxamic acid of suberic acid was 900 mg (95%). ^1H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 8.89 (s, broad, NHOH, 1H); 3.57 (s, CH_3, 3H); 2.27 (t, J=7.4 Hz, CH_2COOCH_3, 2H); 1.91 (t, J=7.4 Hz, $CH_2CONHOH$, 2H); 1.49 (m, 4H), 1.24(m, 4H).



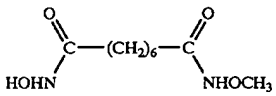
Suberic acid monobenzyloxyamide monomethyl ester (1 g; 3.4 mmol) and potassium hydroxide (210 mg; 3.75 mmol) were dissolved in 10 mL of methanol-water (4:1) mixture. The reaction mixture was refluxed two hours and solvent was evaporated. The solid residue was dissolved in 5 mL water and acidified with conc. hydrochloric acid to pH~5. White precipitate was filtered, dried and crystallized from ethyl acetate-hexanes. The yield of suberic acid monobenzyloxyamide was 820 mg (86%). The product was dissolved in methanol (50 mL) and 5% Pd-C (50 mg) was added. The reaction mixture was shaken under hydrogen pressure (50 psi) overnight. The catalyst was separated by filtration and filtrate was evaporated. The solid residue was slurried in hexanes and filtered. The yield of suberic acid monohydroxamic acid was 520 mg (81%). ^1H NMR (DMSO-d_6, 200 MHz), δ(ppm) 11,96 (s, broad, COOH, 1H); 10.31 (s, NHOH, 1H); 8.63 (s, broad NHOH, 1H); 2.17 (s, J=7.4 Hz, CH_2COOH, 2H); 1.91 (s, $CH_2CONHOH$, 2H); 1.46 (m, 4H); 1.22 (m, 4H).

Compounds having the structure:

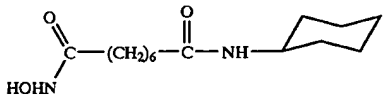


General Procedure

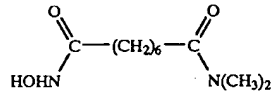
A pyridine (500 mL) solution of O-benzylhydroxylamine (2.46 g; 0.02 mol), the corresponding amine (0.02 mol) and suberoyl chloride was stirred at room temperature overnight. The solvent was evaporated and the semisolid residue was dissolved in 100 mL chloroform-methanol (4:1); the resulting solution was washed with water (2×100 mL), 10% hydrochloric acid (3×100 L), and again with water (2×100 mL). Organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was dissolved in methanol (100 mL) and 5% Pd-C was added. The black suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was separated by filtration, and the filtrate was evaporated. The target products were isolated by column chromatography on silica gel with ethyl acetate-tetrahydrofuran.



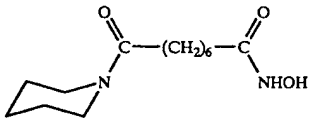
Yield 1.1 g (26%). ^1H NMR (DMSO-D_2, 200 MHz), δ(ppm) 10.93 (s, $NHOCH_3$, 1H); 10.32 (s, NHOH, 1H); 8.66 (s, NHOH, 1H); 3.55 (s, CH_3, 3H); 1.19 (t, J=7.6 Hz, CH_2CO—,4H); 1.45 (m, 4H); 1.20 (m, 4H).



Yield 1.2 g (21%). ^1H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 8.60 (s, broad, NHOH, 1H); 7.57 (d, J=7.6 Hz, NH—C_6H_{11}, 1 H), 3.40 (m, CH—NH, 1H); 1.99 (t, J=7Hz, $CH_2CONHC_6H_{11}$, 2H; 1.91 (t, J=7.6 Hz, $CH_2CONHOH$, 2H); 2.63 (m, 4H); 1.44 (m, 6H); 1.20 (m, 8H).

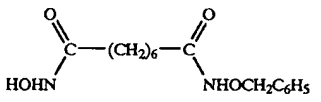


Yield 870 mg (20%); ^1H NMR (DMSO-D_6, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 8.67 (s, broad, NHOH, 1H); 2.85 (d, J=30 Hz, $N(CH_3)_2$, 6H); 2.24 (t, J=7.4 Hz, $CH_2CON(CH_3)$, 2H); 1.91 (t, J=7.4 Hz, $CH_2COONHOH$, 2H); 1.50 (m, 4H); 1.20 (m, 4H).



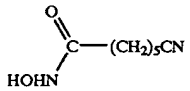
Yield 1.4 g (27%) ^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 8.67 (s, NHOH, 1H); 3.40 (2t, CH_2N, 4H); 2.20 (t, J=7.4 Hz, $CH_2CON(CH_2)_5$, 2H); 1.91 (t, J=7.4 Hz, $CH_2CONHOH$, 2H); 1.10–1.60 (m, broad, 14H).

Compound having structure:



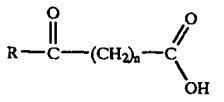
The chloroform (500 mL) solution of O-benzylhydroxylamine (1.23 g; 0.01 mol), O-(trimethylsilyl)hydroxylamine (1.1 g; 0.01 mol), pyridine (1.6 mL; 1.7 g; 0.02 mol) and suberoyl chloride (1.8 mL; 2.11 g; 0.01 mol) was stirred at room temperature overnight. The reaction suspension was diluted with methanol (100 mL), washed with 10% hydrochloric acid (3×100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was subjected to chromatography on silica gel in ethyl acetate-tetrahydrofuran (4:1). The yield was 500 mg (17%). ^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 11.09 (s, $NHOCH_2C_6H_5$, 1H); 10.31 (s, NHOH, 1H); 8.67 (s, broad, NHOH, 1H); 7.36 (s, C_6H_5, 5H), 4.76 (s, $CH_2C_6H_5$, 2H); 1.92 (t, J=7.4 Hz, CH_2CO—, 4H); 1.45 (m, 4H); 1.20 (m, 4H).

Compound having the structure:



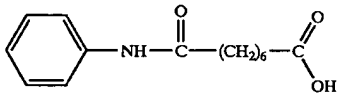
Into a cooled solution of potassium hydroxide (2.24 g; 0.04 mol) and O-benzylhydroxylamine hydrochloride in 30 mL of tetrahydrofuran-water (1:1) mixture, 6-bromohexanoyl chloride (3.1 mL; 4.27 g; 0.02 mol) was added. The reaction mixture was stirred at room temperature for one hour. The solvent was evaporated and solid residue was partitioned between chloroform (200 mL) and water (100 mL). Chloroform layer was washed with 10% hydrochloric acid (3×50 mL) and water (2×50 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The product was purified by crystallization from ethyl acetate-hexanes. The yield of N-benzyloxy-6-bromohexanoyl amide was 4.7 g (78%). A dimethylsulfoxide (250 mL) solution of N-benzyloxy-6-bromohexanoyl amide (4.5 g; 15 mmol) and sodium cyanide (7.35 g; 0.15 mol) was heated at 130° C. overnight. The solvent was evaporated and solid residue was partitioned between chloroform (300 mL) and water (300 mL). The chloroform layer was washed with water (5×100 mL), dried over anhydrous magnesium sulfate, and evaporated. The oily residue was purified by column chromatography on silica gel in ethyl acetate-tetrahydrofuran (4:1) as an eluent. The yield of N-benzyloxy-6-cyanohexanoylamide was 1.62 g (43%). The product was dissolved in methanol (50 mL) and 5% Pd-C (100 mg) was added. The black suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was isolated by filtration and filtrate was evaporated. The solid residue was slurried in hexanes (~20 mL) and filtered. The yield of N-hydroxy-6-cyanohexanoylamide was 900 mg (overall yield 30%). ^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.32 (s, NHOH, 1H); 8.65 (s, NHOH, 1H); 2.45 (t,J=7 Hz, CH_2CN, 2H) 1.93 (t, J=7 Hz, $CH_2CONHOH$, 2H); 1.49 (m, 4H); 1.33 (m, 2H).

Compounds having the structure:

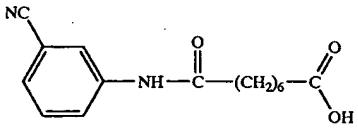


General Procedure

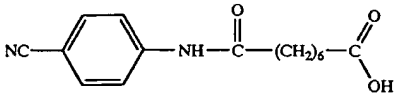
A diacid dichloride (0.01 mol) was added into a cooled (0° C.) solution of potassium hydroxide (1.12 g: 0.02 mol) and corresponding amine (0.01 mol) in 30 mL of tetrahydrofuran-water (1:1) mixture. The reaction mixture was stirred at room temperature about one hour. Solvent was evaporated and the solid residue was partitioned between chloroform (300 mL) and water (300 mL). In some cases a small amount of methanol is necessary to dissolve all solid. The organic layer was washed with 10% potassium hydroxide (3×30 mL). The basic water extract was acidified with 10% hydrochloric acid. The precipitate was collected by filtration, dried and purified by crystallization from ethyl acetate or by column chromatography on silica gel in ethyl acetate-tetrahydrofuran (4:1). The yields are from 20–37%.



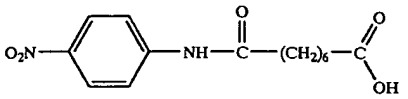
1H NMR (DMSO-d_6, 200 MHz), δ(ppm) 11.97 (s, COOH, 1H); 9.84 (s, NH, 1H); 7.57 (d, J=7.4 Hz, ortho aromatic protons, 2H); 7.26 (t, J=8.4 Hz, meta aromatic protons 2H); 6.99 (t, J=7.4 Hz, para aromatic proton, 1H), 2.27 (t, J=7 Hz, $CH_2CONHPh$, 2H); 2.18 (t, J=7.2 Hz, 2H); 1.52 (m, 4H); 1.28 (m, 4H).



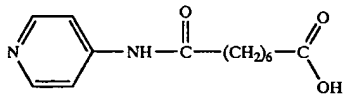
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 11.95 (s, COOH, 1H); 10.20 (s, NH, 1H); 8.10 (s, aromatic proton, 1H); 7.75 (m, aromatic proton, 1H); 7.45 (m, aromatic proton, 2H); 2.28 (t, J=7.4 Hz, $CH_2CONHAr$, 2H); 2.21 (t, J=7.2 Hz, CH_2COOH, 2H); 1.46 (m, 4H); 1.20 (m, 4H).



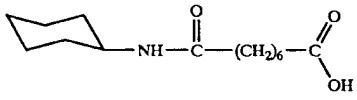
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 11.95 (s, COOH, 1H); 10.29 (s, NH, 1H); 7.75 (s, aromatic protons, 4H); 2.33 (t, J=7.2 Hz, $CH_2CONHAr$, 2H); 2.18 (t, J=7.4 Hz, CH_2COOH, 2H); 1.53 (m, 4H); 1.27 (m, 4H).



^{1}H NMR (DMSO-D_6, 200 MHz), 11.98 (s, broad, COOH, 1H); 10.48 (s, NH, 1H); 8.21 (d, J=9.2 Hz, aromatic protons, 2H); 7.82 (d, J=9.2 Hz, aromatic proton 2H); 2.36 (t, J=7.4 Hz, $CH_2CONHAr$, 2H); 2.18 (t, J=7.2 Hz, CH_2COOH, 2H); 1.55 (m, 4H); 1.29 (m, 4H).

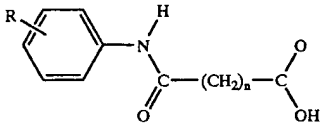


^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 12.00 (s, broad COOH, 2H); 10.24 (s, NH, 1H); 8.38 (d, J=5.8 Hz, aromatic protons, 2H); 7.55 (d, J=5.8 Hz, aromatic protons, 2H); 2.33 (t, J=7.2 Hz, $CH_2CONHAr$, 2H); 2.18 (t, J=7.2 Hz, CH_2COOH); 1.52 (m, 4H); 1.27 (m, 4H).

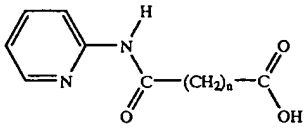


^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 11.95 (s, COOH, 1H); 7.58 (d, J=8 Hz); 3.50 (m, CH, 1H); 2.17 (t, J=7.2 Hz, CH_2COOH, 2H); 2.00 (t, J=7 Hz, CH_2CONH—, 2H); 1.60 (m, 4H); 1.46 (m, 6H); 1.20 (m, 8H).

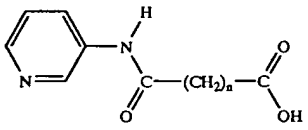
In the same way the following compounds were prepared and characterized:



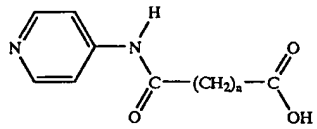
wherein N=4, 5, 6, 7, and 8; R is hydrogen; 2-, 3-, and 4-cyano; 2-, 3-, and 4-nitro; 2-, 3-, and 4-methylcyano; 2-, 3-, and 4-trifluoromethyl; 2-, 3-, and 4-fluoro:



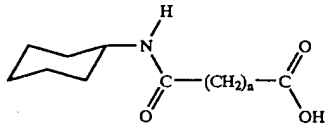
wherein n=4, 5, 6, 7, and 8:



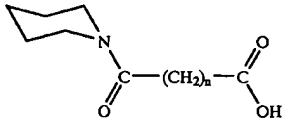
wherein n=4, 5, 6, 7, and 8;



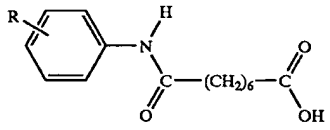
wherein n=4, 5, 6, 7, and 8;



wherein n=4, 5, 6, 7, and 8;

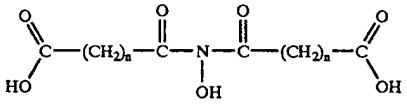


wherein n=4, 5, 6, 7, and 8;



wherein R is 2-, 3-, and 4-carboxy; 2-, 3-, and 4-aminocarbonyl; 2-, 3-, and 4-methylaminocarbonyl; 2-, 3-, and 4-dimethylaminocarbonyl; 2-, and 3-, and 4-chloro; 2-, 3-, and 4-bromo; 2-, 3-, and 4- iodo; 2-, 3-, and 4-methyl; 2-, 3-, and 4-methoxy; 2-, 3-, and 4-hydroxyl; 2-, 3-, and 4-amino; and 2-, 3-, and 4-dimethylamino.

Compounds having the general structure:



wherein n=4, 5, 6, and 7.

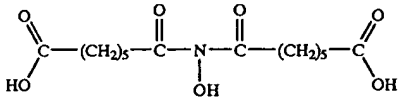
General Procedure A

A pyridine (500 mL) suspension of O-benzylhydroxylamine hydrochloride (3.2 g; 0.02 mol) and the corresponding diacid dichloride (0.04 mol) was stirred at room temperature for three days. Water (10 mL) was added and stirring was continued overnight. The solvent was evaporated and solid residue was purified by column chromatography on silica gel in tetrahydrofuran-methanol. The diacid produce was dissolved in methanol (100 mL) and 5% Pd-C (100 mg) was added. The reaction suspension was shaken overnight under hydrogen pressure (~50 psi). The catalyst was separated by filtration, solid residue was washed with hot methanol (5x50 ml). The combined methanolic filtrates were evaporated. The solid residue was slurried in acetone and filtered. The yield was 10–20%.

General procedure B

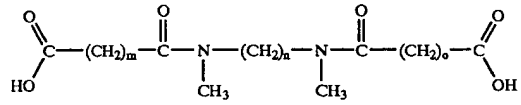
A pyridine (500 ml) solution of O-benzylhydroxylamine (2.46 g; 0.02 mol) and the corresponding dicarboxylic acid

monobenzyl ester monoacid chloride (0.04 mol) was stirred at room temperature overnight. The solvent was evaporated. The semisolid residue was dissolved in chloroform (300 mL) and extracted with 5% hydrochloric acid (2×50 mL), 10% potassium hydroxide (3×100 mL), and water (2×100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was purified by column chromatography on silica gel in ethyl acetate. The tribenzyl product was dissolved in methanol (100 mL) and 5% Pd-C (100 mg) was added. The reaction suspension was shaken under hydrogen pressure (~50 psi) at room temperature overnight. The solid was separated by filtration and washed with hot methanol (5×50 mL). The combined methanol filtrates were evaporated to solid residue. The solid residue was slurried in cooled acetone and filtered. The yield of target product was 30–60%.

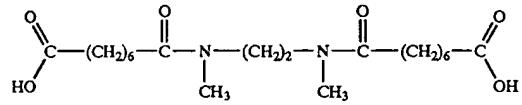


^{1}H NMR (DMSO-d_6, 200MHz), δ(ppm) 11.53 (s, COOH, 1H); 2.41 (t, J=7.2 Hz, $CH_2CON(OH)COCH_2$, 4H); 2.18 (t, J=7.0 Hz, CH_2COOH, 4H); 1.52 (m, 8 h); 1.22 (m, H). MS (FAB, glycerin) 346(M+1)

Compounds having the structure:

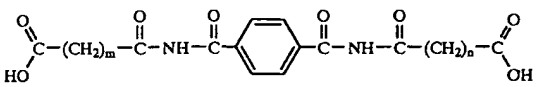


A pyridine (500 mL) solution of the monomethyl ester monoacid chloride of dicarboxylic acid (0.02 mol) and N,N'-dimethyl-1, x-diaminoalkane (0.01 mol) was stirred at room temperature overnight. Solvent was evaporated and oily residue was dissolved in chloroform (300 mL). Chloroform solution was washed with water (3×50 mL), 10% potassium hydroxide (3×50 mL), 10% hydrochloric acid (3×50 mL), and again with water (3×50 mL). The organic layer was dried and evaporated. The oily residue was dissolved in potassium hydroxide (1.2 g; 0.021 mol) in 80% methanol (100 mL). The reaction mixture was refluxed two hours. The solvent was evaporated and solid residue was dissolved in water (50 mL) and extracted with chloroform (3×50 mL). Water solution was acidified to pH~5 and concentrated (to volume of about 10 mL). The water solution or suspension was cooled down and precipitate was separated by filtration. The solid product was purified by crystallization from ethyl acetate. The yield was 40–60%.



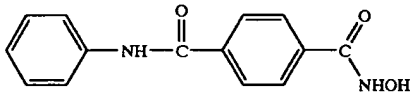
^{1}H NMR ($CDCl_2$, 200 MHz), δ(ppm) 8.15 (s, broad, COOH, 2H); 3.52+3.45 (2s, CH_2N, 4H); 3.01+2.93 (2s, CH_3N, 6H); 2.30 (4t, CH_2CO, 8H); 1.60 (m, 8H); 1.32 (m, 8H). ^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 3.44+3.336+3.36 (3s, CH_2N, 4H); 2.94+2.90+2.79 (3s, CH_2N, 6H); 2.27+2.23 +2.12 (3t, CH_2CO, 8H); 1.46 (m, 8H); 1.23 (m, 8H).

Compounds having the structure:



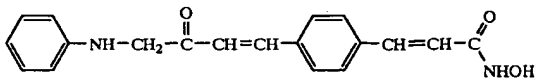
A pyridine (500 mL) solution of 6-aminocapric acid (2.6 g; 0.02 mol) and terephthaloyl chloride (2g; 0.01 mol) was stirred at room temperature overnight (~12 hours), and at 90° C. for 23 hours. The solvent was evaporated, and the solid residue was crystallized from water (10 mL) four times. The yield was 800 mg (19%). ^{1}H NMR (DMSO-d_6, 200 MH), δ(ppm) 12.8 (s, broad, COOH, 2H); 8.54+7.72 (2t, NH, 2H); 3.24+2.98 (2m, $NHCH_2$, 4H); 220+2.03 (2m, CH_2CO, 4H); 1.50 (m, 8H); 1.32 (m, 4H).

Compound having the structure:



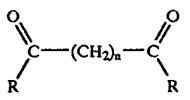
Into a mixture of aniline (2.75 g; 0.03 mol), hydroxylamine hydrochloride (2.08 g; 0.03 mol), and potassium hydroxide (5.50 g; 0.09 mol) in 50% tetrahydrofuran (100 mL) was slowly added at room temperature a tetrahydrofuran (20 mL) solution of terephthaloyl chloride (6g; 0.03 mol). The reaction suspension was stirred at room temperature for thirty minutes. The solvent was evaporated. The solid residue was slurried in hot methanol (1000 mL) and dried over anhydrous magnesium sulfate. The methanol solution was separated by filtration and filtrate was evaporated. The solid residue was slurried in 20 mL cooled methanol and filtered. The white crystals were washed with ether (5×50 mL) and dried. The yield was 4.6 g (39%). ^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 11.35 (s, broad, NHOH, 1H); 10.35 (s, NHPh, 1H); 9.19 (s, NHOH, 1H); 8.03 (d, J=8 Hz, terephthalic protons, 2H); 7.89 (d, J=8 Hz, terephthalic protons, 2H); 7.82 (d, J=7.4 Hz, ortho anilide protons, 2H); 7.34 (t, =7.4 Hz, meta anilide protons, 2H); 7.10 (t, J=7.4 Hz, para anilide proton, 1H).

Compound having the structure:



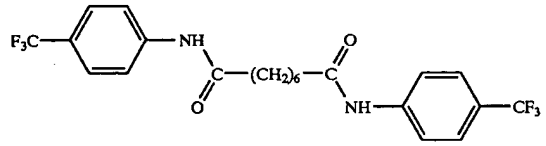
A solution of 1,4-phenylenediacrylic acid (2.18 g; 0.01 mol) in thionyl chloride (50 mL; 8.55 g; 0.68 mol) was refluxed overnight. The excess of thionyl chloride was evaporated. The solid was dissolved in tetrahydrofuran (20 mL), and added to a cooled (0° C.) solution of potassium hydroxide (1.12 g; 0.02 mol) and aniline in 50% tetrahydrofuran. The reaction mixture was stirred at room temperature for thirty minutes. The solvent was evaporated. The solid residue was slurried in water and filtered. White crystals were dissolved in a small amount of methanol and purified on a silica gel column in tetrahydrofuran. The yield was 315 mg (10%). ^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.80 (s, NHOH, 1H); 10.23 (s, NHPh, 1H); 9.09 (s, NHOH, 1H); 7.69 (d, J=7.6 Hz, ortho anilide protons, 2H); 7.64 (s, phenylene protons, 4H), 7.55 (d, J=15.8 Hz, PhNHOCCH=CH—, 1H); 7.40 (d, J=15.8 Hz, HONHOCCH=CH—, 1H); 7.33 (t, J=7.8 Hz, meta anilide protons, 2H); 7.06 (t, J=7.2 Hz, para anilide protons, 1H); 6.89 (d, J=15.8 Hz, PhNHOCCH=CH—, 1H) 6.51 (d, J=15.8 Hz, HOHNOCCH=CH—, 1H).

Compounds having the structure:

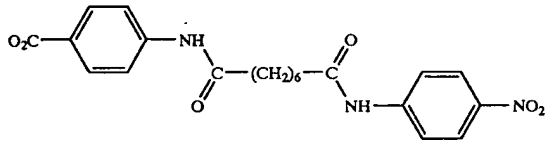


wherein n=4, 5, 6, 7, and 8.

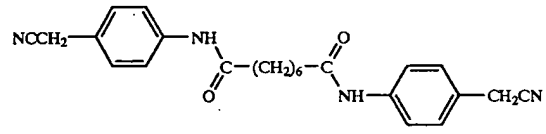
A chloroform solution of triethylamine (1.4 mL; 1.0 g; 0.01 mol), the corresponding amine (0.01 mol) and diacid dichloride (0.005 mol) was stirred at room temperature for five hours. If the reaction mixture was clear, it was washed with water (5x100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated to a solid residue. If in the course of reaction a precipitate was formed, the precipitate was separated by filtration. White crystals from filtration or solid residue from evaporation were crystallized from ethyl acetate, tetrahydrofuran, methanol, or their mixture. The yields were from 60–90%.



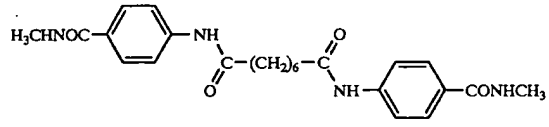
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.23 (s, NH, 2H); 7.82 (d, J=9 Hz, aromatic protons, 4H), 7.60 (d, J=9 Hz, aromatic protons, 4H), 2.31 (t, J=7.4 Hz, CH_2CO, 4H); 2.61 (m, 4H); 1.32 (m, 4H),



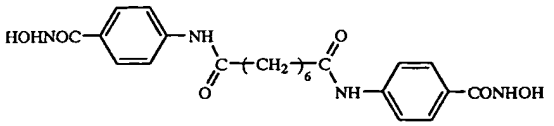
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.48 (s, NH, 2H); 8.18 (d, J=9.2 Hz, aromatic protons, 4H); 7.81 (d, J=9.2 Hz, aromatic protons, 4H0; 2.37 (t, J=7.2 Hz, CH_2CO—, 4H); 1.60 (m, 4H); 1.33 (m, 4H),



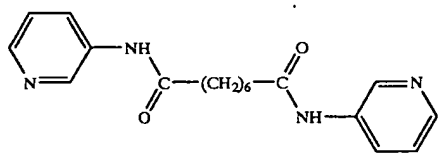
^{1}H NMR (DMSO-$d_6$200 MHz), δ9.91 (s, NH, 2H), 7.58 (d, J=8.6 Hz, aromatic protons, 4H); 7.26 (d, J=8.6 Hz, aromatic protons, 4H); 3.94 (s, CH_2CN, 4H); 2.29 (t, J=7.4 Hz, CH_2CO—, 4H); 1.60 (m, 4H); 1.31 (m, 4H).



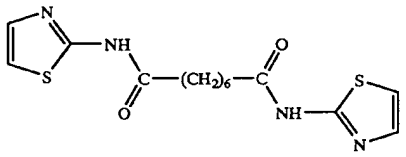
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.08 (s, CONHAr, 2H); 7.79 (d, J=8.6 Hz, aromatic protons, 4H); 7.63 (d, J=8 Hz, aromatic protons, 4H), 7.22 (s, H_3CHNCO—, 2H); 3.32 (s, CH_3, 6H); 2.31 (t, J=7 Hz, CH_2C—), 6H); 1.59 (m, 4H); 1.31 (m, 4H).



^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.90 (s, broad, NHOH, 2H); 10.05 (s, NHAr, 2H); 8.90 (s, broad, NHOH, 2H); 7.68 (d, J=9 Hz, aromatic protons, 4H); 7.62 (d, J=9 Hz, aromatic protons, 4H); 2.31 (t, J=7.2 Hz, CH_2CO—, 4H); 1.59 (m, 4H); 1.30 (m, 4H).

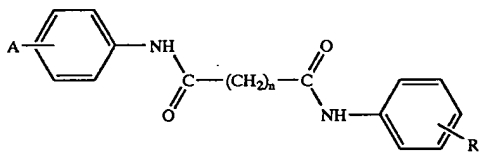


^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.06 (s, broad, NH, 2H); 8.71 (d, J=2.6 Hz, aromatic protons, 2H); 7.31 (d+d, aromatic protons, 2H); 2.32 (t, J=7.4 Hz, CH_2CO—, 4H); 1.59 (m, 4H); 1.33 (m, 4H).

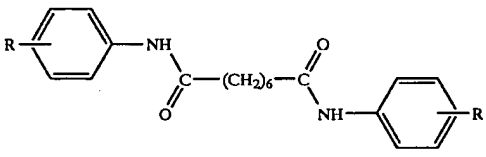


^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 12.00 (s, broad, NH, 2H); 7.43 (d, J=3.6 Hz, aromatic protons, 2H); 7.16 (d, J=3.6 Hz, aromatic protons 2H); 2.41 (t, J=7.2 Hz, CH_2CONH—, 4H) 1.58 (m, 4H); 1.28 (m, 4H).

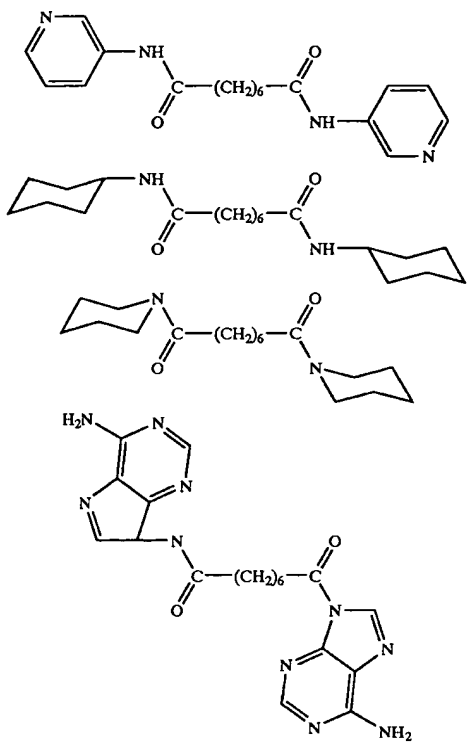
In the similar manner, the following compounds were prepared and characterized:



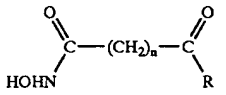
wherein n=4, 5, 6, 7, and 8; all compounds are symmetrical wherein R is 2-, 3-, and 4-cyano; 2-, 3-, and 4-methylcyano; 2-, 3-, and 4-nitro, 2-, 3-, and 4-carboxy; 2-, 3-, and 4-aminocarbonyl; 2-, 3-, and 4-methylaminocarbonyl; 2-, 3-, and 4-dimethylaminocarbonyl; and 2-, 3-, and 4-trifluoromethyl;



wherein R is 4-hydroxylaminocarbonyl; 4-methoxycarbonyl; 2-, 3-, and 4-chloro; 2-, 3-, and 4-fluoro; 2-, 3-, and 4-methyl; 2-, 3-, and 4-methoxy; 2,3-difluoro; 2,4-difluoro; 2,5-difluoro; 2,6-difluoro; 1,2,3,-trifluoro, 3,4,5-trifluoro; 2,3,5,6-tetrafluoro; 2,3,4,5,6-pentafluoro



Compounds having the structure:



wherein n=4, 5, 6, 7, and 8.

General procedure A

A diacid dichloride (0.01 mol) as added to a stirred solution of potassium hydroxide (1.68 g; 0.03 mol), hydroxylamine hydrochloride (0.7 g; 0.01 mol), and the corresponding aniline (0.01 mol) in 50 % tetrahydrofuran (100 mL). The resulting reaction mixture was stirred at room temperature thirty minutes, and solvent was evaporated to solid residue. The solid residue was slurried in methanol (~100 mL) and dried over anhydrous magnesium sulfate. The methanol solution was separated by filtration and evaporated to a solid residue. The product was purified by column chromatography on silica gel in ethyl acetate-tetrahydrofuran (in most cases 3:1). The yields were 15–30%.

General procedure B

A solution of corresponding monomethyl ester of dicarboxylic acid (0.01 mol), oxaloyl chloride (0.03 mol), and a few drops DMF in benzene (500 mL) was stirred at room temperature overnight. The solvent was evaporated and the oily residue was dissolved in dry benzene (3x50 mL) and evaporated again. The tetrahydrofuran (50 mL) solution of monoester monoacid chloride of the corresponding dicarboxylic acid was slowly added to a cooled solution of the corresponding amine (0.01 mol) and pyridine (1.6 mL; 1.6 g; 0.02 mol) in tetrahydrofuran (200 mL). The reaction mixture was stirred at room temperature for an hour. The solvent was evaporated, the reside was dissolved in chloroform (300 mL), and the chloroform solution was washed with 10% hydrochloric acid (3x50 mL), 10% potassium hydroxide (3x50 mL), and water (3x50 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated, yielding the pure monoester monoamide of dicarboxylic acid. The product was dissolved in 80% methanol with potassium hydroxide (0.56 g; 0.01 mol). The reaction mixture was refluxed two hours and evaporated to solid residue. The residue was dissolved in water (~20 mL) and acidified to ~pH 5 with 10% hydrochloric acid. The monoacid monoamide of the dicarboxylic acid was isolated by filtration of precipitate or extraction water solution with chloroform. The isolated monoacid monoamide of the dicarboxylic acid was mixed together with an equivalent amount of O-benzylhydroxylamine and 1,3-dicyclohexylcarbodiimide in pyridine (~100 mL per 0.01 mol of O-benzylhydroxylamine) and was stirred at room temperature overnight. The solvent was evaporated and the solid residue was partitioned between chloroform (500 mL) and 10% hydrochloric acid (300 mL). The organic layer was washed with water (3x100 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to solid residue. The solid residue was dissolved in large amounts of tetrahydrofuran and filtered through a short column of silica gel. The crude product was dissolved in methanol (100 mL) and 5% Pd-C was added. The reaction suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was separated by filtration and filtrate was evaporated to solid residue. The solid residue was slurried in hexanes and filtered. Mostly pure product was isolated in this way. If necessary further purification was achieved by column chromatography on silica gel with ethyl acetate-tetrahydrofuran. The yields were from 35% to 65%.

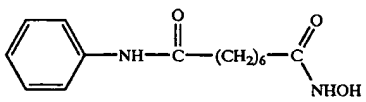
General procedure C

A pyridine (500 mL solution of O-benzylhydroxylamine (1.23; 0.01 mol), the corresponding amine (0.01 mol), and the dichloride of the dicarboxylic acid (0.01 mol) was stirred at room temperature overnight. The solvent was evaporated and the white solid residue contains, judged by ^{1}H NMR, two symmetrical amides and a target unsymmetrical one. The solid residue was slurried in methanol and dried over anhydrous magnesium sulfate. The filtrate was evaporated and the solid residue was dissolved in methanol (~100 mL). Into the methanol solution 5% Pd-C (100 mg) was added and the black suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was separated by filtration and the filtrate was evaporated. The product was isolated by column chromatography on silica with ethyl acetate-tetrahydrofuran. The yields were from 20% to 35%.

General procedure D

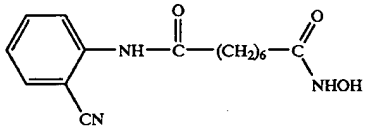
A chloroform solution of triethylamine (3mL; 2.18 g; 0.0215 mol), the corresponding amine (0.01 mol), O-trimethylsilyl)hydroxylamine (1.05 g, 0.01 mol), and the corresponding diacid chloride of the dicarboxylic acid (0.01 mol) was stirred at room temperature overnight. The solvent was evaporated, the residue was dissolved in methanol (~10 mL), and into the methanol solution 10% ammonium chloride (~10 mL) was added. The resulting suspension was stirred at 50° C. for two hours. The solvent was evaporated. The solid residue was slurried in methanol (300 mL) and

dried over anhydrous magnesium sulfate. The methanol solution was separated by filtration and evaporated to a solid residue. The product was isolated by silica gel column chromatography with ethyl acetate-tetrahydrofuran. The yields were 20–33%.

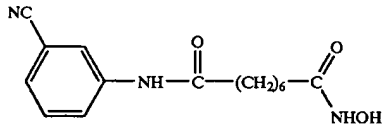


		C	H	N
Elemental analysis:	Calc.	63.62	7.63	10.60
	Found	63.58	7.59	10.48

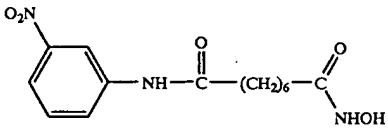
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 9.83 (s, NHPh, 1H); 8.64 (d, NHOH, 2H); 7.57 (d, J=8.2 Hz, ortho aromatic protons, 2H); 7.26 (t, J=8.4 Hz, meta aromatic protons, 2H), 6.99 (t, J=7.4 Hz, para aromatic protons, 1H); 2.27 (t, J=7.4 Hz, $CH_2CONHPh$, 2H); 1.93 (t, J=7.2 Hz, $CH_2CONHOH$, 2H); 1.52 (m, 4H); 1.26 (m, 4H). MS (Fab, Glycerin) 172, 204, 232, 249, 265, (100% M+1).



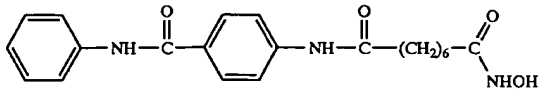
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 10.08 (s, NHPh, 1H); 8.64 (s, NHOH, 1H); 7.78 (d, J=7.6 Hz, aromatic protons, 1H); 7.66 (t, J=7.4 Hz, aromatic protons, 1H); 7.48 (d, J=7.8 Hz, aromatic protons, 1H); 7.29 (t, J=7.4 Hz, aromatic protons, 1H); 2.34 (t, J=7 Hz, $CH_2CONHAr$, 2H); 1.93 (t, J=7.4 Hz, $CH_2CONHOH$, 2H); 1.58 (m, 4H); 1.27 (m, 4H).



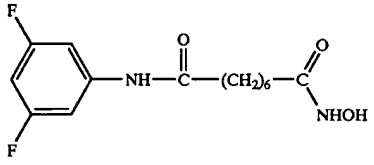
^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 10.21 (s, NHPh, 1H); 8.65 (s, NHOH, 1H); 8.09 (s, aromatic proton, 1H); 7.77 (m, aromatic proton, 1H); 7.49 (m, aromatic proton, 1H); 2.31 (t, J=7.2 Hz, $CH_2CONHAr$, 2H); 1.93 (t, J=7.2 Hz, $CH_2CONHOH$, 2H); 1.51 (m, 4H).



^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.35 (s, NHAr, 1H); 10.31 (s, NHOH, 1H); 8.63 (s, NHOH-+aromatic proton 2H); 7.88 (d, J=8 Hz, aromatic protons 2H); 7.57 (t, J=8 Hz, aromatic proton, 1H); 2.33 (t, J=7.6 Hz, $CH_2CONHAr$, 2H); 1.93 (t, J=7.4 Hz, $CH_2CONHOH$, 2H), 1.52 (m, 4H); 1.27 (m, 4H),

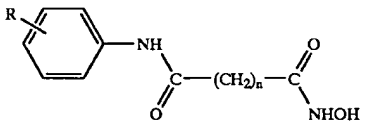


^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.33 (s, NHOH, 1H); 10.15 (s, NHAr, 1H); 10.09 (s, NHPh, 1H); 8.66 (s, NHOH, 1H); 7.91 (d, J=8.6 Hz, aromatic protons 2H); 7.76 (d, J=7.8 Hz, ortho aniline protons, 2H); 7.71 (d, J=8.6 Hz, aromatic protons, 2H); 7.33 (t, J=7.6 Hz, meta anilide protons, 2H); 7.07 (t, J=7.4 Hz, para anilide protons); 2.33 (t, J=7.5 Hz, CH_2NHAr, 2H); 1.93 (t, J=7.2 Hz, CH_2CNHH, 2H); 1.51 (m, 4H); 1.28 (m, 4H).

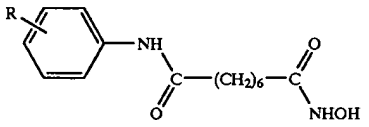


^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 10.32 (s, NHOH, 1H); 10.21 (s, NHAr, 1H); 8.65 (s, NHOH, 1H); 7.31 (d of d, J=10 Hz(2.2 Hz), aromatic protons, 2H); 6.84 (t of t, J=9.4 Hz(2.4Hz), aromatic protons, 1H); 2.29 (t, $CH_2CONHAr$, 2H); 1.93 (t, J=7.2 Hz, $CH_2CONHOH$, 2H); 1.51 (m, 4H); 1.26 (m, 4H).

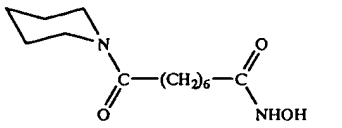
In the same manner the following compounds were prepared and characterized:



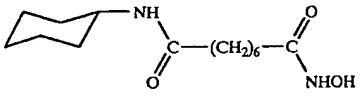
wherein n=4, 5, 6, 7, and 8; and R is 2-, 3-, and 4-cyano; 2-, 3-, and 4-methylcyano; 2-, 3-, and 4-nitro; 2-, 3-, and 4-carboxy; 2-, 3-, and 4-aminocarbonyl; 2-, 3-, and 4-methylaminocarbonyl; 2-, 3-, and 4-dimethylaminocarbonyl; and 2-, 3-, and 4-trifluoromethyl;



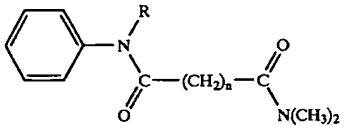
wherein R is 4-hydroxylaminocarbonyl; 4-methoxycarbonyl; 4-tetrazoyl; 2-, 3-, and 4-chloro; 2-, 3-, and 4-fluoro; 2-, 3-, and 4-methyl; 2-, 3-, and 4-methoxy; 2,3-difluoro; 2,4-difluoro; 2,5-difluoro; 2,6-difluoro; 1,2,3-trifluoro; 3,4,5-trifluoro; 2,4,5-trifluoro; 2,4,6-trifluoro; 2,3,6-trifluoro; 2,3,5,6-trifluoro; 2,3,4,5,6-pentafluoro; 2-, 3-, and 4-phenyl; 2-, 3-, and 4-benzyloxy; 4-hexyl; and 4-t-butyl;



-continued

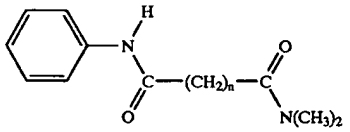


Compounds having the structure

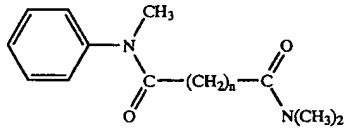


wherein n=4, 5, 6, 7, and 8; and R is hydrogen or methyl.

A diacid dichloride (0.01 mol) was added into a stirred solution of potassium hydroxide (1.68 g; 0.03 mol), aniline or N-methylaniline (0.01 mol), and dimethylamine hydrochloride (0.805 g; 0.01 mol) in 50% tetrahydrofuran (100 mL). The reaction mixture was stirred thirty minutes at room temperature. The solvent was partitioned between chloroform (400 mL) and water (300 mL). The organic layer was washed with 10% hydrochloric acid (3x100 mL), 10% potassium hydroxide (3x100 mL), and water (2x100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was slurried in hexanes and filtered. The yield were 25–34%.



^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 9.82 (s, NHPh, 1H); 7.58 (d, J=7.6 Hz, ortho aromatic protons, 2H); 7.26 (t, J=7.4 Hz, meta aromatic protons, 2H); 6.99 (t, J=7.4 Hz, para aromatic proton, 1H); 2.85 (d, J=28 Hz, $N(CH_3)_2$, 6 H); 2.28 (t, J=7.2 Hz, CH_2CO, 2H); 2.24 (t, J=7.4 Hz, CH_2CO, 2H); 1.51 (m, 4H); 1.29 (m, 4H).



^{1}H NMR (DMSO-d_6, 200 MHz), δ(ppm) 7.30 (m, C_6H_5, 5H); 3.13 (s, H_3CNPh, 3H); 2.83 (d, J=26 Hz, $N(CH_3)_2$, 6H); 2.17 (t, J=7.6 Hz, $CH_2CON(CH_3)_2$, 2H); 1.98 (t, J=7.4 Hz, $CH_2CON(CH_3)Ph$, 2H); 1.41 (m, 4H); 1.11 (m, 4H).

TABLE 1

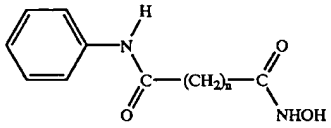
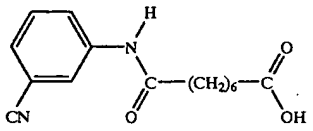
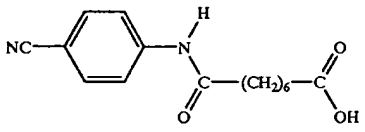
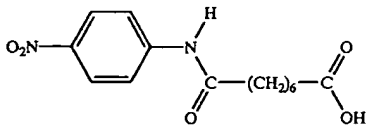
CPD	Structure	Mol. Weight	Optimal Conc. (μM)	Benzidine Reactive Cells (%)
				
1	n = 4 (known compound)	236	80	70
2	n = 5	250	20	84
3	n = 6	264	2.5	70
4	n = 7	278	20	8
5	n = 8	292	20	15
6		274	31	44
7		274	31	52
8		294	12.5	32

TABLE 1-continued

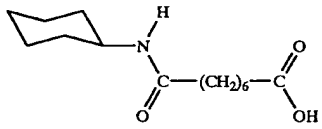
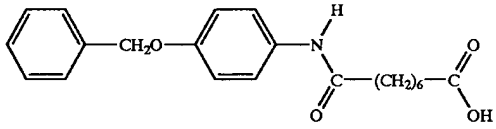
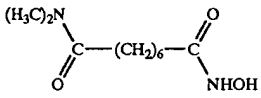
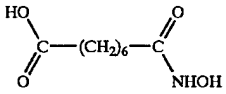
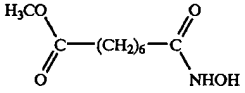
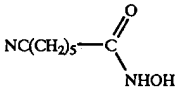
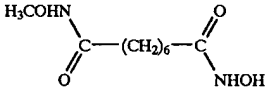
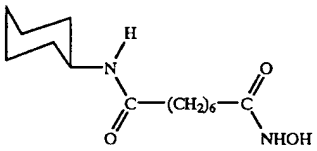
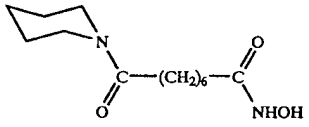
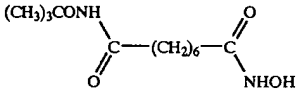
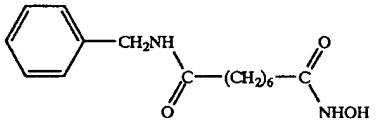
CPD	Structure	Mol. Weight	Optimal Conc. (μM)	Benzidine Reactive Cells (%)
9		225	50	20
10		355	250	26
11		216	60	53
12		189	250	35
13		203	60	17
14		156	125	30
15		218	20	43
16		270	8	35
17		256	62	30
18		260	31	38
19		278	5	24

TABLE 1-continued

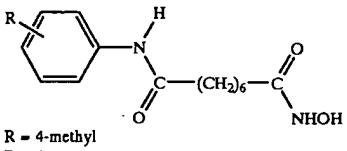
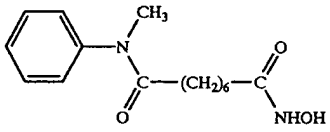
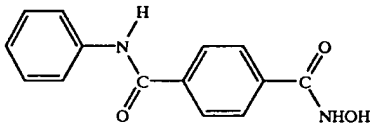
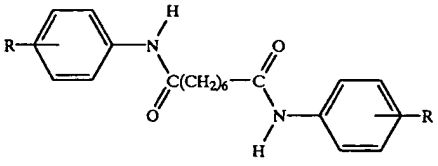
CPD	Structure	Mol. Weight	Optimal Conc. (μM)	Benzidine Reactive Cells (%)
				
20	R = 4-methyl	273	20	52
21	R = 4-cyano	289	7	70
22	R = 3-cyano	289	5	55
23	R = 2-cyano	289	16	65
24	R = 3-nitro	309	5	30
25	R = 4-nitro	309	0.8	30
26	R = 3-trifluoromethyl	332	30	30
27	R = 4-trifluoromethyl	332	5	47
28	R = 2-amino	279	20	54
29	R = 4-cyanomethyl	303	1	30
30	R = 3-chloro	298.5	2	33
31	R = 4-azido (N_3)	304	2	47
32	R = 2-fluoro	282	4	65
33	R = 3-fluoro	282	1	25
34	R = 4-fluoro	282	4	43
35	R = 4-benzyloxy	370	4	20
36	R = 4-methyoxycarbonyl	322	4	28
37	R = 4-methylaminocarbonyl	321	30	16
38	R = 2-bromo	343	8	45
39	R = 2-chloro	298.5	4	34
40	R = 4-bromo	343	1.6	47
41	R = 2,3-difluoro	300	8	24
42	R = 2,4,5-trifluoro	318	8	36
43	R = 2,3,6-trifluoro	318	31	53
44	R = 2,4,6-trifluoro	318	16	47
45	R = 2,4-difluoro	300	6	60
46	R = 2,3,4,5,6-pentafluoro	354	31	53
47	R = 3,4-difluoro	300	4	61
48	R = 3,4,5-trifluoro	318	8	55
49	R = 2,5-difluoro	300	4	70
50	R = 3,5-difluoro	300	2	73
51	R = 2-methoxy	294	8	36
52	R = 3-methoxy	294	6	38
53	R = 4-methoxy	294	6	37
54		290	20	40
55		256	30	53
				
56	R = tri-fluoromethyl	460	50	20
57	R = 4(N)-hydroxylaminocarbonyl	442	8	10
58	R = 4-cyanomethyl	402	50	25
59	R = 2,4-difluoro	396	500	54
60	R = 2,6-difluoro	396	100	21
61	R = 3,5-difluoro	396	125	31
62	R = 2,3,6-trifluoro	432	250	28
63	R = 2,4,6-trifluoro	432	125	35
64	R = 2,3,4,5,6-pentafluoro	504	125	13
65	R = 4-nitro	414	25	14

TABLE 1-continued

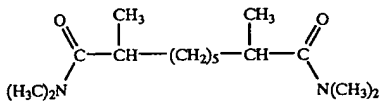
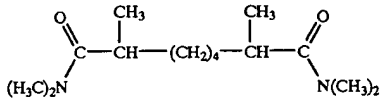
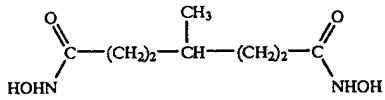
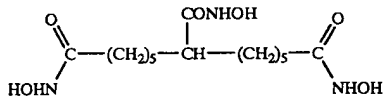
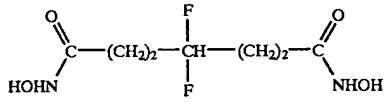
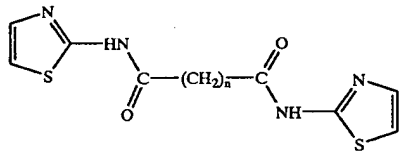
CPD	Structure	Mol. Weight	Optimal Conc. (μM)	Benzidine Reactive Cells (%)
66		270	1250	80
67		256	2500	90
68		204	125	56
69		333	60	40
70		226	160	19
71	 n = 4	310	100	8
72	n = 5	324	250	10
73	n = 6	338	50	7
74	n = 7	352	100	10
75	n = 8	366	100	10

TABLE 2

	Induction of Differentiation of HL-60		
CPD	Mol. Weight	Optimal Conc. (μM)	NBT Positive (%)
2	250	7	22
3	264	1	21
6	274	20	30
7	274	20	21
22	289	1.7	28
21	289	2	6
26	332	6	27
25	309	3	18
36	322	1	32
31	304	2.5	7
29	303	1	15
43	318	2	20

References

1. Sporn, M. B., Roberts, A. B., and Driscoll, J. S. (1985) in Cancer: Principles and Practice of Oncology, eds. Hellman, S., Rosenberg, S. A., and DeVita, V. T., Jr., Ed. 2, (J. B. Lippincott, Philadelphia), P. 49.

2. Breitman, T. R., Selonick, S. E., and Collins, S. J. (1980) Proc. Natl. Acad. Sci. USA 77: 2936–2940.

3. Olsson, I. L. and Breitman, T. R. (1982) Cancer Res. 42: 3924–3927.

4. Schwartz, E. L. and Sartorelli, A. C. (1982) Cancer Res. 42: 2651–2655.

5. Marks, P. A., Sheffery, M., and Rifkind, R. A. (1987) Cancer Res. 47: 659.

6. Sachs, L. (1978) Nature (Lond.) 274: 535.

7. Friend, C., Scher, W., Holland, J. W., and Sato, T. (1971) Proc. Natl. Acad. Sci. (USA) 68: 378–382.

8. Tanaka, M., Levy, J., Terada, M., Breslow, R., Rifkind, R. A., and Marks, P. A. (1975) Proc. Natl. Acad. Sci. (USA) 72: 1003–1006.

9. Reuben, R. C., Wife, R. L., Breslow, R., Rifkind, R. A., and Marks, P. A. (1976) Proc. Natl. Acad. Sci. (USA) 73: 862–866.

10. Abe, E. Miyaura, C., Sakagami, H., Takeda, M., Konno K., Yamazaki, T., Yoshika, S., and Suda, T. (1981) Proc. Natl. Acad, Sci. (USA) 78: 4990–4994.

11. Schwartz, E. L., Snoddy, J. R., Kreutter, D., Rasmussen, H., and Sartorelli, A. C. (1983) Proc. Am. Assoc. Cancer Res. 24: 18.

12. Tanenaga, K., Hozumi, M., and Sakagami, Y. (1980) Cancer Res. 40: 914–919.

13. Lotem, J. and Sachs, L. (1975) Int. J. Cancer 15: 731–740.

14. Metcalf, D. (1985) Science, 229: 16–22.

15. Scher, W., Scher, B. M., and Waxman, S. (1983) Exp. Hematol. 11: 490–498.

16. Scher, W., Scher, B. M., and Waxman, S. (1982) Biochem. & Biophys. Res. Comm. 109: 348–354.

17. Huberman, E. and Callaham, M. F. (1979) Proc. Natl. Acad. Sci. (USA) 76: 1293–1297.

18. Lottem, J. and Sachs, L. (1979) Proc. Natl. Acad. Sci. (USA) 76: 5158–5162.

19. Terada, M., Epner, E., Nudel, U., Salmon, J., Fibach, E., Rifkind, R. A., and Marks, P. A. (1978) Proc. Natl. Acad. Sci. (USA) 75: 2795–2799.

20. Morin, M. J. and Sartorelli, A. C. (1984) Cancer Res. 44: 2807–2812.

21. Schwartz, E. L., Brown, B. J., Nierenberg, M., Marsh, J. C., and Sartorelli, A. C. (1983) Cancer Res. 43: 2725–2730.

22. Sugano, H., Furusawa, M., Kawaguchi, T., and Ikawa, Y. (1973) Bibl. Hematol. 39: 943–954.

23. Ebert, P. S., Wars, I., and Buell, D. N. (1976) Cancer Res. 36: 1809–1813.

24. Hayashi, M., Okabe, J., and Hozumi, M. (1979) Gann 70: 235–238.

25. Fibach, E., Reuben, R. C., Rifkind, R. A., and Marks, P. A. (1977) Cancer Res. 37: 440–444.

26. Melloni, E., Pontremoli, S., Damiani, G., Viotti, P., Weich, N., Rifkind, R. A., and Marks, P. A. (1988) Proc. Natl. Acad. Sci. (USA) 85: 3835–3839.

27. Reuben, R., Khanna, P. L., Gazitt, Y., Breslow, R., Rifkind, R. A., and Marks, P. A. (1978) J. Biol. Chem. 253: 4214–4218.

28. Marks, P. A. and Rifkind, R. A. (1988) International Journal of Cell Cloning 6: 230–240.

29. Melloni, E., Pontremoli, S., Michetti, M., Sacco, O., Cakiroglu, A. G., Jackson, J. F., Rifkind, R. A., and Marks, P. A. (1987) Proc. Natl. Acad. Sciences (USA) 84: 5282–5286.

30. Marks, P. A. and Rifkind, R. A. (1984) Cancer 54: 2766–2769.

31. Egorin, M. J., Sigman, L. M. VanEcho, D. A., Forrest, A., Whitacre, M. Y., and Aisner, J. (1987) Cancer. Res. 47: 617–623.

32. Rowinsky, E. W., Ettinger, D. S., Grochow, L. B., Brundrett, R. B., Cates, A. E., and Donehower, R. C. (1986) J. Clin. Oncol. 4: 1835–1844.

33. Rowinsky, E. L. Ettinger, D. S., McGuire, W. P., Noe, D. A., Grochow, L. B., and Donehower, R. C. (1987) Cancer Res. 47: 5788–5795.

34. Callery, P. S., Egorin, M. J., Geelhaar, L. A., and Nayer, M. S. B. (1986) Cancer Res. 46: 4900–4903.

35. Young, C. W. Fanucchi, M. P., Walsh, T. B., Blatzer, L., Yaldaie, S., Stevens, Y. W., Gordon, C., Tong, W., Rifkind, R. A., and Marks, P. A. (1988) Cancer Res. 48: 7304–7309.

36. Andreeff, M., Young, C., Clarkson, B., Fetten, J., Rifkind, R. A., and Marks, P. A. (1988) Blood 72: 186a.

37. Marks, P. A., Breslow, R., Rifkind, R. A., Ngo, L., and Singh, R. (1989) Proc. Natl. Acad. Sci. (USA) 86: 6358–6362.

38. Breslow, R., Jursic, B., Yan, Z. F., Friedman, E., Leng, L., Ngo, L., Rifkind, R. A., and Marks, P. A. (1991) Proc. Natl. Acad. Sci. (USA) 88: 5542–5546.

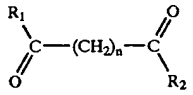
39. Ohta, Y., Tanaka, M., Terada, M., Miller, O. J., Bank, A., Marks, P. A., and Rifkind, R. A. (1976) Proc. Natl. Acad. Sci. (USA) 73: 1232–1236.

40. Collins, S. J., Gallo, R. C., and Gallagher, R. E. (1978) Nature (London) 270: 405–409.

41. Synder, S. W., Egorin, M. J., Geelhaar, L. A., Hamburger, A. W., and Callery, P. S. (1988) Cancer Res. 48; 3613–3616.

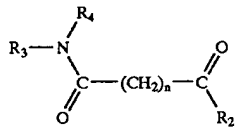
What is claimed is:

1. A compound having the structure:



wherein [each of R_1 and R_2 are independently the same as or different from each other; when] R_1 and R_2 are the same[, each is] *and are* a substituted or unsubstituted [cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or] thiazoleamino group; [when R_1 and R_2 are different, R_1=R_3—N—R_4, wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group and R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, or alkyloxy group;] and n is an integer from about 4 to about 8.

2. A compound of [claim 1] having the structure:



wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino[, hydroxyl, amino, alkylamino, or alkyloxy] group; [and] n is an integer from [about 4] *5* to [about 8] *7; and R_3—N—R_4 and R_2 are different.*

3. A compound of claim 2, wherein [R_2 is a hydroxylamino, hydroxyl, amino, methylamino, or methoxy group and] n is 6.

4. A compound of claim 3, wherein R_4 is a hydrogen atom and R_3 is a substituted or unsubstituted phenyl group.

5. A compound of claim 4, wherein the phenyl group is substituted with a methyl, cyano, nitro, trifluoromethyl, amino, aminocarbonyl, metylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, [methyoxy] *methoxy*, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, [methyoxycarbonyl] *methoxycarbonyl*, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

6. A compound of claim 3, wherein R_4 is a hydrogen atom and R_3 is a cyclohexyl group.

7. A compound of claim 3, wherein R_4 is a hydrogen atom and R_3 is a [methyoxy] *methoxy* group.

8. A compound of claim 3, wherein R_3 and R_4 bond together to form a piperidine group.

[9. A compound of claim 3, wherein R_4 is a hydrogen atom and R_3 is a hydroxyl group.]

10. A compound of claim 3, wherein R_4 is a hydrogen atom and R_3 is a benzyloxy group.

11. A compound of claim [3] 2, wherein R_4 is a hydrogen atom and R_3 is a [δ-pyridine] *γ-pyridine* group.

12. A compound of claim [3] 2, wherein R_4 is a hydrogen atom and R_3 is a β-pyridine group.

13. A compound of claim [3] 2, wherein R_4 is a hydrogen atom and R_3 is a α-pyridine group.

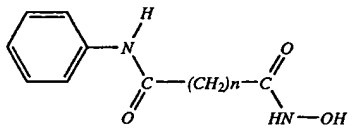
14. A compound of claim 3, wherein R_3 and R_4 are both methyl groups.

15. A compound of claim 3, wherein R_4 is a methyl group and R_3 is a phenyl group.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 2.

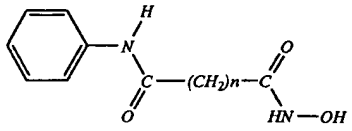
17. A pharmaceutical composition of claim 16 in combination with an antitumor agent.

18. A compound having the structure:



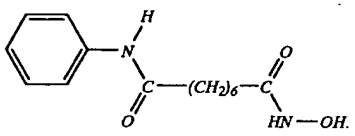
wherein n is an integer selected from the group consisting of 5, 6, 7 and 8.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound having the structure:

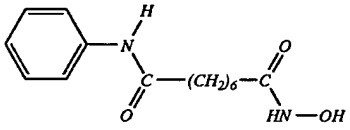


wherein n is an integer selected from the group consisting of 5, 6, 7 and 8: and a pharmaceutically acceptable carrier.

20. A compound having the structure:

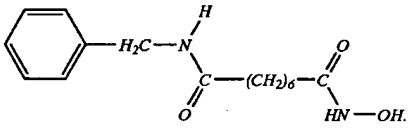


21. A pharmaceutical composition comprising a therapeutically effective amount of a compound having the structure:

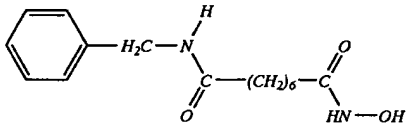


and a pharmaceutically acceptable carrier.

22. A compound having the structure:

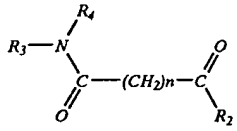


23. A pharmaceutical composition comprising a compound having the structure:



and a pharmaceutically acceptable carrier.

24. A compound having the structure:



wherein R_3 is hydrogen and R_4 cycloalkyl, aryl, aryloxy, arylalkloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino group; and n is an integer selected from the group consisting of 5, 6, 7 and 8.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

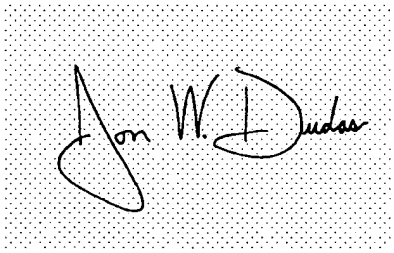
PATENT NO. : RE 38,506 E
APPLICATION NO. : 10/004411
DATED : April 20, 2004
INVENTOR(S) : Breslow et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 5, column 36, line 58, "metylcyano" should read -- methylcyano --.

Signed and Sealed this

Twenty-ninth Day of August, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

2.

DATE: 01/30/92
TO:
COOPER & DUNHAM
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS, ON THIS NOTICE, PLEASE SEND A REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR:
BRESLOW, RONALD
DOC DATE: 11/24/91

ASSIGNOR:
RIFKIND, RICHARD A.
DOC DATE: 11/27/91

ASSIGNOR:
JURSIC, BRANKO
DOC DATE: 11/27/91

ASSIGNOR:
MARKS, PAUL A.
DOC DATE: 11/27/91

RECORDATION DATE: 12/09/91 NUMBER OF PAGES 007 REEL/FRAME 5935/0910

DIGEST :ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
A CORPORATION OF NY
1275 YORK AVENUE
NEW YORK, NEW YORK 10021

ASSIGNEE:
TRUSTEES OF COLUMBIA UNIVERSITY, THE
A CORPORATION OF NY
WEST 116TH STREET & BROADWAY
NEW YORK, NEW YORK 10027

SERIAL NUMBER	7-771760	FILING DATE	10/04/91
PATENT NUMBER		ISSUE DATE	00/00/00

Dkt. 26472-G

A S S I G N M E N T

In consideration of One Dollar ($1.00), and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the undersigned,

Ronald Breslow, Paul A. Marks, Richard A. Rifkind, and Branko Jursic, residing at 275 Broad Avenue, Englewood, New Jersey 07631, Beach Hill Road, Bridgewater, Connecticut 06752, 30 Sutton Place, New York, New York 10022, and 91 Spanish Fort Boulevard, New Orleans, Louisiana 70124, respectively;

Hereby do sell, assign and transfer to Sloan-Kettering Institute for Cancer Research, a Corporation of the State of New York, having a place of business at 1275 York Avenue, in the County of New York and State of New York 10021, and to The Trustees of Columbia University in the City of New York, a corporation of the State of New York, having a place of business at West 116th Street & Broadway, in the County of New York and State of New York 10027, as joint owners, to their title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on November 18, 24, and 27, 1991
and is entitled:

NOVEL POTENT INDUCERS OF TERMINAL
DIFFERENTIATION AND METHOD OF USE THEREOF
(U.S. Serial No. 771,760, filed October 4, 1991)

and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for U.S. Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorizes and requests the Commissioner of Patents of the United States to issue to said Assignees, the corporations above named, their successors, assigns and legal representatives,

in accordance with the assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;

Agrees that said Assignees may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; that, when requested to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigneds' executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignees, their successors, assigns and representatives, all facts known and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignees, their successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all patents on said inventions, in said Assignees, their successors, assigns and legal representatives; and

COVENANTS with said Assignees, their successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.

Date: 11/24/91
Witness
William S Jeboks
530 Riverside Dr #4J
New York, NY 10027-3425

[L.S.]
Ronald Breslow

Date:
Witness

[L.S.]
Paul A. Marks

in accordance with the assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;

Agrees that said Assignees may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; that, when requested to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigneds' executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignees, their successors, assigns and representatives, all facts known and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignees, their successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all patents on said inventions, in said Assignees, their successors, assigns and legal representatives; and

COVENANTS with said Assignees, their successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.

Date:_____
Witness_____
_____
_____
_____

_____[L.S.]
Ronald Breslow

Date: ~~11-26-91~~ 11/27/91
Witness ~~Paul A. Marks~~ Carol L. McCluskey
~~1275 York Road~~
~~Warminster, PA 18974~~ 118-184 Ave
Kongarden, NY

Paul A. Marks [L.S.]
Paul A. Marks

Date: 11/27/91
Witness Carol L. McCluskey
CAROL L. McCLUSKEY
118-11 84th Ave
Kew Gardens, NY 11415

Richard A. Rifkind [L.S.]

Date:
Witness

Branko Jursic [L.S.]

Date:_____
Witness_____

_____[L.S.]
Richard A. Rifkind

Date: 11/18/91
Witness Jack W Timberlake
Chemistry Dept
University of New Orleans
New Orleans, LA 70148

_____[L.S.]
Branko Jursic

Dennis M Erb, Ph D
Vice President
Global Strategic Regulatory Development

Merck & Co . Inc
P O Box 1000, UG2D-78
North Wales PA 19454-1099
Tel 267 305 6768
Fax 267 305 6469
dennis_erb@merck com

3

November 21, 2006

MERCK
Research Laboratories

The Trustees of Columbia University
in the City of New York
Office of General Counsel
412 Low Memorial Library
535 W 116th St.
Mail code 4308
New York, NY 10027

Sloan-Kettering Institute for Cancer Research
Office of Industrial Affairs
1275 York Avenue
New York, NY 10021

To Whom It May Concern:

This letter is to confirm that Merck & Co., Inc. ("Merck") specifically authorizes The Trustees of Columbia University in the City of New York and Sloan-Kettering Institute for Cancer Research to rely on Merck's activities before the FDA in connection with Merck's application under 21 U.S.C. § 355(b) for approval to market Zolinza™ for the purposes of an application to extend the term, under 35 U.S.C. § 156, of U.S. Patent No. RE38,506 E, which is co-owned by The Trustees of Columbia University in the City of New York and Sloan-Kettering Institute for Cancer Research.

Sincerely,

Dennis M. Erb.

Dr. Dennis M. Erb, Ph.D
Vice President
Global Strategic Regulatory Development

4.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	**U.S. Patent No.: RE38,506 E, issued April 20, 2004; Reissue of 5,369,108, issued November 29th, 1994**
Issued:	**November 29th, 1994**
To:	**Ronald Breslow, Paul A. Marks, Richard A. Rifkind, Branko Jursic**
Assignee:	**Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York**
Title:	**Potent Inducers of Terminal Differentiation and methods of use thereof**

MAIL STOP HATCH-WAXMAN PTE
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313- 1450

AUTHORIZATION OF AGENT AND NEW POWER OF ATTORNEY

Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York, owners of the above-identified United States Patent No. RE38,506, filed October 4, 1991, assignment recorded on December 9, 1991, at Reel/Frame: 5935/0910, hereby appoints the attorneys and/or agents associated with Mintz Levin Cohn Ferris Glovsky & Popeo, Customer Number 30623, as Applicants' attorneys of Sloan-Kettering Institute for Cancer Research and of The Trustees of Columbia University in the City of New York with regard to an application for extension of term of U.S. Patent No. RE38,506 and to transact all actions necessary with regard to the above-identified patent term extension application.

Please address all telephone calls to Ivor R. Elrifi at telephone number 617/348-1747. Please address all correspondence to:

30623

PATENT TRADEMARK OFFICE

Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York certify under 37 C.F.R. § 3.73(b) that they are the Assignees of the entire right, title and interest in the patent application identified above by virtue of assignments of the patent identified above.

We, the undersigned, are empowered to act on behalf of Assignees Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York, respectively. Acting on behalf of the Assignees, we have reviewed all the documents in the chain of title of the patent application identified above and, to the best of our knowledge and belief, title is in the Assignees identified above.

We, the undersigned, hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the patent.

Please charge any fee or any fee deficiency occasioned by this document to Deposit Account No. 50-0311, Attorney Reference No. 24852-500(Customer Number: 30623).

Respectfully submitted,

MICHAEL J. CLEARE, PhD.
Executive Director
Science & Technology Ventures

NAME:
TITLE:
COMPANY: The Trustees of Columbia University in the City of New York

Date: November 29th, 2006

NAME:
TITLE:
COMPANY: Sloan-Kettering Institute for Cancer Research

Date: November __, 2006

TRA 2224996v.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	**U.S. Patent No.: RE38,506 E, issued April 20, 2004; Reissue of 5,369,108, issued November 29th, 1994**
Issued:	**November 29th, 1994**
To:	**Ronald Breslow, Paul A. Marks, Richard A. Rifkind, Branko Jursic**
Assignee:	**Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York**
Title:	**Potent Inducers of Terminal Differentiation and methods of use thereof**

MAIL STOP HATCH-WAXMAN PTE
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313- 1450

AUTHORIZATION OF AGENT AND NEW POWER OF ATTORNEY

Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York, owners of the above-identified United States Patent No. RE38,506, filed October 4, 1991, assignment recorded on December 9, 1991, at Reel/Frame: 5935/0910, hereby appoints the attorneys and/or agents associated with Mintz Levin Cohn Ferris Glovsky & Popeo, Customer Number 30623, as Applicants' attorneys of Sloan-Kettering Institute for Cancer Research and of The Trustees of Columbia University in the City of New York with regard to an application for extension of term of U.S. Patent No. RE38,506 and to transact all actions necessary with regard to the above-identified patent term extension application.

Please address all telephone calls to Ivor R. Elrifi at telephone number 617/348-1747. Please address all correspondence to:

30623

PATENT TRADEMARK OFFICE

Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York certify under 37 C.F.R. § 3.73(b) that they are the Assignees of the entire right, title and interest in the patent application identified above by virtue of assignments of the patent identified above.

We, the undersigned, are empowered to act on behalf of Assignees Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University in the City of New York, respectively. Acting on behalf of the Assignees, we have reviewed all the documents in the chain of title of the patent application identified above and, to the best of our knowledge and belief, title is in the Assignees identified above.

We, the undersigned, hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the patent.

Please charge any fee or any fee deficiency occasioned by this document to Deposit Account No. 50-0311, Attorney Reference No. 24852-500(Customer Number: 30623).

Respectfully submitted,

NAME:
TITLE:
COMPANY: The Trustees of Columbia University in the City of New York

Date: November __, 2006

NAME: Roger N. Parker, JD ~~Esq.~~
TITLE: Senior Vice President and General Counsel
COMPANY: Sloan-Kettering Institute for Cancer Research

Date: November 29, 2006

TRA 2224996v.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-991

Merck & Co., Inc.
Attention: Randi Albin, Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
RY32-605
Rahway, NJ 07065

Dear Dr. Albin:

Please refer to your new drug application (NDA) dated April 5, 2006, received April 7, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zolinza (vorinostat) Capsules, 100 mg.

We acknowledge receipt of your submissions dated December 6, 2005; February 22, 2006; April 5, 2006; June 19, 28, and 30, 2006; July 14, 21, and 28, 2006; August 4, 8, and 28, 2006; September 6, 8, 13, 18, 22, 25, 26 and 29, 2006; and October 2, and 4, 2006.

This new drug application provides for the use of Zolinza (vorinostat) Capsules for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.

An expiration dating period of 24 months is granted for this product.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, and, immediate container labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-991.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated October 4, 2006. These commitments are listed below.

Commitment 1:
Merck commits to provide updates of the exposure and safety data (adverse experiences leading to dose interruption, dose modification, or dose discontinuation) collected for CTCL patients who initially received vorinostat on Protocol 001 and continued to receive vorinostat on Protocol 007. A report will be provided annually starting in October 2007 and will continue until the final CTCL patient discontinues from Protocol 007 or for a maximum of 3 years.

First Report Submission: October 2007
Final Report Submission: October 2009

Commitment 2:
Merck agrees to conduct a pharmacokinetic study in cancer patients with hepatic impairment. Merck will submit the protocol to the agency prior to conduct of the study for agreement with the study design. Merck will conduct this pharmacokinetic study in the advanced cancer patient population with mild to moderate hepatic insufficiency, according to the Child-Pugh classification or the NCI criteria. Pharmacokinetic sample collection will occur after single-dose administration. The minimum target sample size will be approximately 4. If the study cannot be fully enrolled, the study will be closed after completion of the moderate impairment cohort.

Protocol Submission Date: April 1, 2007
Study Start (study enrollment open): October 1, 2007
Final Report Submission: October 2012

Commitment 3:
Merck agrees to study the effect of vorinostat on the ECG QT interval in the advanced cancer patient population. Intensive ECG monitoring, as well as pharmacokinetic sampling, will occur at baseline and after single-dose administration. The target sample size will be approximately 18.

Protocol Submission Date: January 1, 2007
Study Start (study enrollment open): April 1, 2007
Final Report Submission: April 2009

Commitment 4:
Merck commits to assess safety and laboratory monitoring data from ongoing Merck studies in patients treated concomitantly with vorinostat and warfarin. A report will be submitted annually starting October 2007 and will continue until data has been analyzed for 40 patients or for a maximum of three years.

First Report Submission Date: October 2007

Final Report Submission: October 2009

Commitment 5:
Merck commits to submit all adverse experiences reported as vorinostat-drug interactions in the post-marketing environment as expedited (15-day) reports. Each adverse experience from Merck clinical trials which meets the criteria of serious according to the regulatory definition and is considered to be a result of a vorinostat-drug interaction will be submitted as an expedited (15-day) report. A summary of these adverse experiences will be submitted annually starting in October 2007 and will continue for three years.

First Report Submission Date: October 2007
Final Report Submission: October 2009

Commitment 6:
Merck commits to conduct two in vitro efflux studies; one to determine whether vorinostat is a substrate of P-glycoprotein and one to determine whether vorinostat is an inhibitor of P-glycoprotein.

Studies Start: December 2006
Final Reports Submission: March 2007

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Paul Zimmerman, Regulatory Project Manager, at (301) 796-1489.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
10/6/2006 02:31:55 PM

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZOLINZA safely and effectively. See full prescribing information for ZOLINZA.

ZOLINZA™ (vorinostat) Capsules
Initial U.S. Approval: 20XX

----------INDICATIONS AND USAGE----------
ZOLINZA is a histone deacetylase (HDAC) inhibitor indicated for:
- Treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies. (1)

----------DOSAGE AND ADMINISTRATION----------
- 400 mg orally once daily with food. (2.1)
- If patient is intolerant to therapy, the dose may be reduced to 300 mg orally once daily with food. If necessary, the dose may be further reduced to 300 mg once daily with food for 5 consecutive days each week. (2.2, 5)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 100 mg (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Pulmonary embolism and deep vein thrombosis have been reported. Monitor patient for pertinent signs and symptoms. (5.1)
- Dose-related thrombocytopenia and anemia have occurred and may require dose modification or discontinuation. (2.2, 5.2, 6)
- Gastrointestinal disturbances (e.g., nausea, vomiting and diarrhea) have been reported. Patients may require antiemetics, antidiarrheals and fluid and electrolyte replacement (to prevent dehydration). (5.3, 6, 17.1)
- Hyperglycemia has been observed. Adjustment of diet and/or therapy for increased glucose may be necessary. (5.4, 5.6)
- QTc prolongation has been observed. Monitor electrolytes and ECGs at baseline and periodically during treatment. (5.5, 5.6)
- Monitor blood cell counts and chemistry tests, including electrolytes, glucose and serum creatinine, every 2 weeks during the first 2 months of therapy and monthly thereafter. (5.6)
- Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (e.g., valproic acid). Monitor platelet count. (5.7, 7.2)
- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus. (5.8)

----------ADVERSE REACTIONS----------
- The most common adverse reactions (incidence ≥20%) are diarrhea, fatigue, nausea, thrombocytopenia, anorexia and dysgeusia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Coumarin-derivative anticoagulants: Prolongation of prothrombin time and International Normalized Ratio have been observed with concomitant use. Monitor carefully. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: X/200X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZOLINZA[1] is indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose is 400 mg orally once daily with food.

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

ZOLINZA capsules should not be opened or crushed *[see How Supplied/Storage and Handling (16)]*.

2.2 Dose Modifications

If a patient is intolerant to therapy, the dose may be reduced to 300 mg orally once daily with food. The dose may be further reduced to 300 mg once daily with food for 5 consecutive days each week, as necessary.

2.3 Dosing in Special Populations

No information is available in patients with renal or hepatic impairment *[see Pharmacokinetics (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

100 mg white, opaque, hard gelatin capsules with "568" over "100 mg" printed within radial bar in black ink on the capsule body.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolism

As pulmonary embolism and deep vein thrombosis have been reported as adverse reactions, physicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of thromboembolic events *[see Adverse Reactions (6)]*.

5.2 Hematologic

Treatment with ZOLINZA can cause dose-related thrombocytopenia and anemia. If platelet counts and/or hemoglobin are reduced during treatment with ZOLINZA, the dose should be modified or therapy discontinued. *[See Dosage and Administration (2.2), Warnings and Precautions (5.6) and Adverse Reactions (6).]*

5.3 Gastrointestinal

Gastrointestinal disturbances, including nausea, vomiting and diarrhea, have been reported *[see Adverse Reactions (6)]* and may require the use of antiemetic and antidiarrheal medications. Fluid and electrolytes should be replaced to prevent dehydration *[see Adverse Reactions (6.1)]*. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before beginning therapy with ZOLINZA.

5.4 Hyperglycemia

Hyperglycemia has been observed in patients receiving ZOLINZA *[see Adverse Reactions (6.1)]*. Serum glucose should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or therapy for increased glucose may be necessary.

5.5 QTc Prolongation

A definitive study of the effect of vorinostat on QTc has not been conducted. Three of 86 CTCL patients exposed to 400 mg once daily had Grade 1 (>450-470 msec) or 2 (>470-500 msec or increase of >60 msec above baseline) clinical adverse events of QTc prolongation. In a retrospective analysis of three Phase 1 and two Phase 2 studies, 116 patients had a baseline and at least one follow-up ECG. Four patients had Grade 2 (>470-500 msec or increase of >60 msec above baseline) and 1 patient had Grade 3 (>500 msec) QTc prolongation. In 49 non-CTCL patients from 3 clinical trials who had complete evaluation of QT interval, 2 had QTc measurements of >500 msec and 1 had a QTc prolongation of >60 msec.

5.6 Monitoring: Laboratory Tests

Careful monitoring of blood cell counts and chemistry tests, including electrolytes, glucose and serum creatinine, should be performed every 2 weeks during the first 2 months of therapy and monthly thereafter. Electrolyte monitoring should include potassium, magnesium and calcium. Baseline and periodic ECGs should be performed during treatment. ZOLINZA should be administered with particular

caution in patients with congenital long QT syndrome, and patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation. Hypokalemia or hypomagnesemia should be corrected prior to administration of ZOLINZA, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g., patients with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms). *[See Warnings and Precautions (5.5).]*

5.7 Other Histone Deacetylase (HDAC) Inhibitors

Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (e.g., valproic acid). Monitor platelet count every 2 weeks during the first 2 months. *[See Drug Interactions (7.2)].*

5.8 Pregnancy

Pregnancy Category D

ZOLINZA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ZOLINZA in pregnant women. Results of animal studies indicate that vorinostat crosses the placenta and is found in fetal plasma at levels up to 50% of maternal concentrations. Doses up to 50 and 150 mg/kg/day were tested in rats and rabbits, respectively (~0.5 times the human exposure based on $AUC_{0\text{-}24\ hours}$). Treatment-related developmental effects including decreased mean live fetal weights, incomplete ossifications of the skull, thoracic vertebra, sternebra, and skeletal variations (cervical ribs, supernumerary ribs, vertebral count and sacral arch variations) in rats at the highest dose of vorinostat tested. Reductions in mean live fetal weight and an elevated incidence of incomplete ossification of the metacarpals were seen in rabbits dosed at 150 mg/kg/day. The no observed effect levels (NOELs) for these findings were 15 and 50 mg/kg/day (<0.1 times the human exposure based on AUC) in rats and rabbits, respectively. A dose-related increase in the incidence of malformations of the gall bladder was noted in all drug treatment groups in rabbits versus the concurrent control. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6 ADVERSE REACTIONS

The most common drug-related adverse reactions can be classified into 4 symptom complexes: gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, constipation), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth). The most common serious drug-related adverse reactions were pulmonary embolism and anemia.

6.1 Clinical Trials Experience

The safety of ZOLINZA was evaluated in 107 CTCL patients in two single arm clinical studies in which 86 patients received 400 mg once daily.

The data described below reflect exposure to ZOLINZA 400 mg once daily in the 86 patients for a median number of 97.5 days on therapy (range 2 to 480+ days). Seventeen (19.8%) patients were exposed beyond 24 weeks and 8 (9.3%) patients were exposed beyond 1 year. The population of CTCL patients studied was 37 to 83 years of age, 47.7% female, 52.3% male, and 81.4% white, 16.3% black, and 1.2% Asian or multi-racial.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions

Table 1 summarizes the frequency of CTCL patients with specific adverse events, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0).

Table 1
Clinical or Laboratory Adverse Events Occurring in CTCL Patients
(Incidence ≥10% of patients)

	ZOLINZA 400 mg once daily (N=86)			
Adverse Events	**All Grades**		**Grades 3-5***	
	n	**%**	**n**	**%**
Fatigue	45	52.3	3	3.5
Diarrhea	45	52.3	0	0.0
Nausea	35	40.7	3	3.5
Dysgeusia	24	27.9	0	0.0
Thrombocytopenia	22	25.6	5	5.8
Anorexia	21	24.4	2	2.3
Weight Decreased	18	20.9	1	1.2
Muscle Spasms	17	19.8	2	2.3
Alopecia	16	18.6	0	0.0
Dry Mouth	14	16.3	0	0.0
Blood Creatinine Increased	14	16.3	0	0.0
Chills	14	16.3	1	1.2
Vomiting	13	15.1	1	1.2
Constipation	13	15.1	0	0.0
Dizziness	13	15.1	1	1.2
Anemia	12	14.0	2	2.3
Decreased Appetite	12	14.0	1	1.2
Peripheral Edema	11	12.8	0	0.0
Headache	10	11.6	0	0.0
Pruritus	10	11.6	1	1.2
Cough	9	10.5	0	0.0
Upper Respiratory Infection	9	10.5	0	0.0
Pyrexia	9	10.5	1	1.2

* No Grade 5 events were reported.

The frequencies of more severe thrombocytopenia, anemia *[see Warnings and Precautions (5.2)]* and fatigue were increased at doses higher than 400 mg once daily of ZOLINZA.

Serious Adverse Reactions

The most common serious adverse events, regardless of causality, in the 86 CTCL patients in two clinical studies were pulmonary embolism reported in 4.7% (4/86) of patients, squamous cell carcinoma reported in 3.5% (3/86) of patients and anemia reported in 2.3% (2/86) of patients. There were single events of cholecystitis, death (of unknown cause), deep vein thrombosis, enterococcal infection, exfoliative dermatitis, gastrointestinal hemorrhage, infection, lobar pneumonia, myocardial infarction, ischemic stroke, pelvi-ureteric obstruction, sepsis, spinal cord injury; streptococcal bacteremia, syncope, T-cell lymphoma, thrombocytopenia and ureteric obstruction.

Discontinuations

Of the CTCL patients who received the 400-mg once daily dose, 9.3% (8/86) of patients discontinued ZOLINZA due to adverse events. These adverse events, regardless of causality, included anemia, angioneurotic edema, asthenia, chest pain, exfoliative dermatitis, death, deep vein thrombosis, ischemic stroke, lethargy, pulmonary embolism, and spinal cord injury.

Dose Modifications

Of the CTCL patients who received the 400-mg once daily dose, 10.5% (9/86) of patients required a dose modification of ZOLINZA due to adverse events. These adverse events included increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia and vomiting. The median time to the first adverse event resulting in dose reduction was 42 days (range 17 to 263 days).

Laboratory Abnormalities

Laboratory abnormalities were reported in all of the 86 CTCL patients who received the 400-mg once-daily dose.

Increased serum glucose was reported as a laboratory abnormality in 69% (59/86) of CTCL patients who received the 400-mg once daily dose; only 4 of these abnormalities were severe (Grade 3). Increased serum glucose was reported as an adverse event in 8.1% (7/86) of CTCL patients who received the 400-mg once daily dose. *[See Warnings and Precautions (5.4).]*

Transient increases in serum creatinine were detected in 46.5% (40/86) of CTCL patients who received the 400-mg once daily dose. Of these laboratory abnormalities, 34 were NCI CTCAE Grade 1, 5 were Grade 2, and 1 was Grade 3.

Proteinuria was detected as a laboratory abnormality (51.4%) in 38 of 74 patients tested. The clinical significance of this finding is unknown.

Dehydration

Based on reports of dehydration as a serious drug-related adverse event in clinical trials, patients were instructed to drink at least 2 L/day of fluids for adequate hydration. *[See Warnings and Precautions (5.3, 5.6).]*

Adverse Reactions in Non-CTCL Patients

The frequencies of individual adverse events were substantially higher in the non-CTCL population. Drug-related serious adverse events reported in the non-CTCL population which were not observed in the CTCL population included single events of blurred vision, asthenia, hyponatremia, tumor hemorrhage, Guillain-Barré syndrome, renal failure, urinary retention, cough, hemoptysis, hypertension, and vasculitis.

7 DRUG INTERACTIONS

7.1 Coumarin-Derivative Anticoagulants

Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) were observed in patients receiving ZOLINZA concomitantly with coumarin-derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered ZOLINZA and coumarin derivatives.

7.2 Other HDAC Inhibitors

Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of ZOLINZA and other HDAC inhibitors (e.g., valproic acid). Monitor platelet count every 2 weeks for the first 2 months. *[See Warnings and Precautions (5.7).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [See Warnings and Precautions (5.8)]

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZOLINZA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ZOLINZA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients with CTCL in trials (N=107), 46 percent were 65 years of age and over, while 15 percent were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Use in Patients with Hepatic Impairment

Vorinostat was not evaluated in patients with hepatic impairment. As vorinostat is predominantly eliminated through metabolism, patients with hepatic impairment should be treated with caution. *[See Clinical Pharmacology (12.3).]*

8.7 Use in Patients with Renal Impairment

Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat. Patients with pre-existing renal impairment should be treated with caution. *[See Clinical Pharmacology (12.3).]*

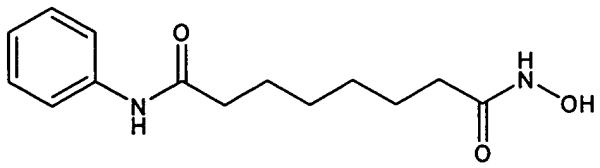
10 OVERDOSAGE

No specific information is available on the treatment of overdosage of ZOLINZA.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. It is not known if vorinostat is dialyzable.

11 DESCRIPTION

ZOLINZA contains vorinostat, which is described chemically as *N*-hydroxy-*N'*-phenyloctanediamide. The empirical formula is $C_{14}H_{20}N_2O_3$. The molecular weight is 264.32 and the structural formula is:



Vorinostat is a white to light orange powder. It is very slightly soluble in water, slightly soluble in ethanol, isopropanol and acetone, freely soluble in dimethyl sulfoxide and insoluble in methylene chloride. It has no chiral centers and is non-hygroscopic. The differential scanning calorimetry ranged from 161.7 (endotherm) to 163.9°C. The pH of saturated water solutions of vorinostat drug substance was 6.6. The pKa of vorinostat was determined to be 9.2.

Each 100 mg ZOLINZA capsule for oral administration contains 100 mg vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vorinostat inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) at nanomolar concentrations (IC_{50}<86 nM). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation. *In vitro*, vorinostat causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells. The mechanism of the antineoplastic effect of vorinostat has not been fully characterized.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of vorinostat were evaluated in 23 patients with relapsed or refractory advanced cancer. After oral administration of a single 400-mg dose of vorinostat with a high-fat meal, the mean ± standard deviation area under the curve (AUC) and peak serum concentration (C_{max}) and the median (range) time to maximum concentration (T_{max}) were 5.5±1.8 μM•hr, 1.2±0.62 μM and 4 (2-10) hours, respectively.

In the fasted state, oral administration of a single 400-mg dose of vorinostat resulted in a mean AUC and C_{max} and median T_{max} of 4.2±1.9 μM•hr and 1.2±0.35 μM and 1.5 (0.5-10) hours, respectively. Therefore, oral administration of vorinostat with a high-fat meal resulted in an increase (33%) in the extent of absorption and a modest decrease in the rate of absorption (T_{max} delayed 2.5 hours) compared to the fasted state. However, these small effects are not expected to be clinically meaningful. In clinical trials of patients with CTCL, vorinostat was taken with food.

At steady state in the fed-state, oral administration of multiple 400-mg doses of vorinostat resulted in a mean AUC and C_{max} and a median T_{max} of 6.0±2.0 μM•hr, 1.2±0.53 μM and 4 (0.5-14) hours, respectively.

Distribution

Vorinostat is approximately 71% bound to human plasma proteins over the range of concentrations of 0.5 to 50 µg/mL.

Metabolism

The major pathways of vorinostat metabolism involve glucuronidation and hydrolysis followed by β-oxidation. Human serum levels of two metabolites, *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid were measured. Both metabolites are pharmacologically inactive. Compared to vorinostat, the mean steady state serum exposures in humans of the *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid were 4-fold and 13-fold higher, respectively.

In vitro studies using human liver microsomes indicate negligible biotransformation by cytochromes P450 (CYP).

Excretion

Vorinostat is eliminated predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine, indicating that renal excretion does not play a role in the elimination of vorinostat. The mean urinary recovery of two pharmacologically inactive metabolites at steady state was 16±5.8% of vorinostat dose as the *O*-glucuronide of vorinostat, and 36±8.6% of vorinostat dose as 4-anilino-4-oxobutanoic acid. Total urinary recovery of vorinostat and these two metabolites averaged 52±13.3% of vorinostat dose. The mean terminal half-life ($t_{½}$) was ~2.0 hours for both vorinostat and the *O*-glucuronide metabolite, while that of the 4-anilino-4-oxobutanoic acid metabolite was 11 hours.

Special Populations

Based upon an exploratory analysis of limited data, gender, race and age do not appear to have meaningful effects on the pharmacokinetics of vorinostat.

Pediatric

Vorinostat was not evaluated in patients <18 years of age.

Hepatic Insufficiency

Vorinostat was not evaluated in patients with hepatic impairment. *[See Use In Specific Populations (8.6).]*

Renal Insufficiency

Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat. *[See Use In Specific Populations (8.7).]*

Pharmacokinetic effects of vorinostat with other agents

Vorinostat is not an inhibitor of CYP drug metabolizing enzymes in human liver microsomes at steady state C_{max} of the 400 mg dose (C_{max} of 1.2 µM vs IC_{50} of >75 µM). Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by vorinostat at concentrations higher (≥10 µM) than pharmacologically relevant. Thus, vorinostat is not expected to affect the pharmacokinetics of other agents. As vorinostat is not eliminated via the CYP pathways, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known CYP inhibitors or inducers. However, no formal clinical studies have been conducted to evaluate drug interactions with vorinostat.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with vorinostat.

Vorinostat was mutagenic *in vitro* in the bacterial reverse mutation assays (Ames test), caused chromosomal aberrations *in vitro* in Chinese hamster ovary (CHO) cells and increased the incidence of micro-nucleated erythrocytes when administered to mice (Mouse Micronucleus Assay).

Effects on the female reproductive system were identified in the oral fertility study when females were dosed for 14 days prior to mating through gestational day 7. Doses of 15, 50 and 150 mg/kg/day to rats resulted in approximate exposures of 0.15, 0.36 and 0.70 times the expected clinical exposure based on AUC. Dose dependent increases in corpora lutea were noted at ≥15 mg/kg/day, which resulted in increased peri-implantation losses were noted at ≥50 mg/kg/day. At 150 mg/kg/day, there were increases in the incidences of dead fetuses and in resorptions.

No effects on reproductive performance were observed in male rats dosed (20, 50, 150 mg/kg/day; approximate exposures of 0.15, 0.36 and 0.70 times the expected clinical exposure based on AUC), for 70 days prior to mating with untreated females. *[See Warnings and Precautions (5.8)]*

14 CLINICAL STUDIES

Cutaneous T-cell Lymphoma

In two open-label clinical studies, patients with refractory CTCL have been evaluated to determine their response rate to oral ZOLINZA. One study was a single-arm clinical study and the other assessed several dosing regimens. In both studies, patients were treated until disease progression or intolerable toxicity.

Study 1

In an open-label, single-arm, multicenter non-randomized study, 74 patients with advanced CTCL were treated with ZOLINZA at a dose of 400 mg once daily. The primary endpoint was response rate to oral ZOLINZA in the treatment of skin disease in patients with advanced CTCL (Stage IIB and higher) who had progressive, persistent, or recurrent disease on or following two systemic therapies. Enrolled patients should have received, been intolerant to or not a candidate for bexarotene. Extent of skin disease was quantitatively assessed by investigators using a modified Severity Weighted Assessment Tool (SWAT). The investigator measured the percentage total body surface area (%TBSA) involvement separately for patches, plaques, and tumors within 12 body regions using the patient's palm as a "ruler". The total %TBSA for each lesion type was multiplied by a severity weighting factor (1=patch, 2=plaque and 4=tumor) and summed to derive the SWAT score. Efficacy was measured as either a Complete Clinical Response (CCR) defined as no evidence of disease, or Partial Response (PR) defined as a ≥50% decrease in SWAT skin assessment score compared to baseline. Both CCR and PR had to be maintained for at least 4 weeks.

Secondary efficacy endpoints included response duration, time to progression, and time to objective response.

The population had been exposed to a median of three prior therapies (range 1 to 12).

Table 2 summarizes the demographic and disease characteristics of the Study 1 population.

Table 2
Baseline Patient Characteristics
(All Patients As Treated)

Characteristics	Vorinostat (N=74)
Age (year)	
Mean (SD)	61.2 (11.3)
Median (Range)	60.0 (39.0, 83.0)
Gender, n (%)	
Male	38 (51.4%)
Female	36 (48.6%)
CTCL stage, n (%)	
IB	11 (14.9%)
IIA	2 (2.7%)
IIB	19 (25.7%)
III	22 (29.7%)
IVA	16 (21.6%)
IVB	4 (5.4%)
Racial Origin, n (%)	
Asian	1 (1.4%)
Black	11 (14.9%)
Other	1 (1.4%)
White	61 (82.4%)
Time from Initial CTCL Diagnosis (year)	
Median (Range)	2.6 (0.0, 27.3)
Clinical Characteristics	
Number of prior systemic treatments, median (range)	3.0 (1.0, 12.0)

The overall objective response rate was 29.7% (22/74, 95% CI [19.7 to 41.5%]) in all patients treated with ZOLINZA. In patients with Stage IIB and higher CTCL, the overall objective response rate was 29.5% (18/61). One patient with Stage IIB CTCL achieved a CCR. Median times to response were 55 and 56 days (range 28 to 171 days), respectively in the overall population and in patients with Stage IIB and higher CTCL. However, in rare cases it took up to 6 months for patients to achieve an objective response to ZOLINZA.

The median response duration was not reached since the majority of responses continued at the time of analysis, but was estimated to exceed 6 months for both the overall population and in patients with Stage IIB and higher CTCL. When end of response was defined as a 50% increase in SWAT score from the nadir, the estimated median response duration was 168 days and the median time to tumor progression was 202 days.

Using a 25% increase in SWAT score from the nadir as criterion for tumor progression, the estimated median time-to-progression was 148 days for the overall population and 169 days in the 61 patients with Stage IIB and higher CTCL.

Response to any previous systemic therapy does not appear to be predictive of response to ZOLINZA.

Study 2

In an open-label, non-randomized study, ZOLINZA was evaluated to determine the response rate for patients with CTCL who were refractory or intolerant to at least one treatment. In this study, 33 patients were assigned to one of 3 cohorts: Cohort 1, 400 mg once daily; Cohort 2, 300 mg twice daily 3 days/week; or Cohort 3, 300 mg twice daily for 14 days followed by a 7-day rest (induction). In Cohort 3, if at least a partial response was not observed then patients were dosed with a maintenance regimen of 200 mg twice daily. The primary efficacy endpoint, objective response, was measured by the 7-point Physician's Global Assessment (PGA) scale. The investigator assessed improvement or worsening in overall disease compared to baseline based on overall clinical impression. Index and non-index cutaneous lesions as well as cutaneous tumors, lymph nodes and all other disease manifestations were also assessed and included in the overall clinical impression. CCR required 100% clearing of all findings, and PR required at least 50% improvement in disease findings.

The median age was 67.0 years (range 26.0 to 82.0). Fifty-five percent of patients were male, and 45% of patients were female. Fifteen percent of patients had Stage IA, IB, or IIA CTCL and 85% of patients had Stage IIB, III, IVA, or IVB CTCL. The median number of prior systemic therapies was 4 (range 0.0 to 11.0).

In all patients treated, the objective response was 24.2% (8/33) in the overall population, 25% (7/28) in patients with Stage IIB or higher disease and 36.4% (4/11) in patients with Sezary syndrome. The overall response rates were 30.8%, 9.1% and 33.3% in Cohort 1, Cohort 2 and Cohort 3, respectively. The 300 mg twice daily regimen had higher toxicity with no additional clinical benefit over the 400 mg once daily regimen. No CCR was observed.

Among the 8 patients who responded to study treatment, the median time to response was 83.5 days (range 25 to 153 days). The median response duration was 106 days (range 66 to 136 days). Median time to progression was 211.5 days (range 94 to 255 days).

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. NIH [2002]. 1999 recommendations for the safe handling of cytotoxic drugs. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. 92-2621.
4. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs.
5. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZOLINZA capsules, 100 mg, are white, opaque hard gelatin capsules with "568" over "100 mg" printed within the radial bar in black ink on the capsule body. They are supplied as follows:

NDC 0006-0568-40.

Each bottle contains 120 capsules.

Storage and Handling

Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-5] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

ZOLINZA (vorinostat) capsules should not be opened or crushed. Direct contact of the powder in ZOLINZA capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed and/or broken capsules *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.2)]

17.1 Instructions

Patients should be instructed to drink at least 2 L/day of fluid to prevent dehydration and should promptly report excessive vomiting or diarrhea to their physician. Patients should be instructed about the signs of deep vein thrombosis and should consult their physician should any evidence of deep vein thrombosis develop. Patients receiving ZOLINZA should seek immediate medical attention if unusual bleeding occurs. ZOLINZA capsules should not be opened or crushed.

Patients should be instructed to read the patient insert carefully.

Manufactured for:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Patheon, Inc.
Mississauga, Ontario, Canada L5N 7K9

Printed in USA

XXXXXXX

U.S. Patent Nos. RE 38,506 E, 6,087,367

17.2 FDA-Approved Patient Labeling

[1]Trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey 08889 USA

Patient Information
ZOLINZA™ (zo LINZ ah)
(vorinostat)
Capsules

Read the patient information that comes with ZOLINZA* before you start taking it and each time you get a refill. There may be new information. This leaflet is a summary of the information for patients. Your doctor or pharmacist can give you additional information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is ZOLINZA?

ZOLINZA is a prescription medicine used to treat a type of cancer called cutaneous T-cell lymphoma (CTCL) in patients when the CTCL gets worse, does not go away, or comes back after treatment with other medicines.

ZOLINZA has not been studied in children under the age of 18.

What should I tell my doctor before taking ZOLINZA?

Tell your doctor about all of your medical conditions, including if you:

- Have any allergies
- Have had a blood clot in your lung (pulmonary embolus)
- Have had a blood clot in a vein (a blood vessel) anywhere in your body (deep vein thrombosis)
- Have nausea, vomiting, or diarrhea
- Have high blood sugar or diabetes
- Have heart problems
- Are pregnant or plan to become pregnant. ZOLINZA may harm your unborn baby. ZOLINZA has not been studied in pregnant women. If you use ZOLINZA during pregnancy, tell your doctor immediately.
- Are breast-feeding or plan to breast-feed. It is not known if ZOLINZA will pass into your breast milk. Talk to your doctor about the best way to feed your baby while you are taking ZOLINZA.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Some medicines may affect how ZOLINZA works, or ZOLINZA may affect how your other medicines work. **Especially tell your doctor if you take:**

- **Valproic acid:** a medicine used to treat seizures. Your doctor will decide if you should continue to take valproic acid and may want to test your blood more frequently.
- **COUMADIN®: (warfarin) or any other blood thinner**. Ask your doctor if you are not sure if you are taking a blood thinner. Your doctor may want to test your blood more frequently.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take ZOLINZA?

- Take ZOLINZA exactly as your doctor tells you to.
- Your doctor will tell you how many ZOLINZA capsules to take and when to take them.
- Swallow each capsule whole. Do not chew or break open the capsule. If you can't swallow ZOLINZA

---

*Trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, 08889 USA

capsules whole, tell your doctor. You may need a different medicine.

- Take ZOLINZA with food.
- If ZOLINZA capsules are accidentally opened or crushed, do not touch the capsules or the powder contents of the capsules. If the powder from an open or crushed capsule gets on your skin or in your eyes, wash the contacted area well with plenty of plain water. Call your doctor.
- **Drink at least eight 8-ounce glasses of liquids every day while taking ZOLINZA.** Drinking enough fluids may help to decrease the chances of losing too much fluid from your body (dehydration) especially if you are having symptoms such as nausea, vomiting or diarrhea while taking ZOLINZA.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is almost time for your next dose, just skip the missed dose. Just take the next dose at your regular time. Do not take two doses of ZOLINZA at the same time.
- If you take too much ZOLINZA, call your doctor, local emergency room, or poison control center right away.
- Your doctor will check your blood cell counts, blood sugar, and other chemistries every two weeks for the first two months of your treatment with ZOLINZA and then monthly. Your doctor may decide to do other tests to check your health as needed.
- If you have high blood sugar (hyperglycemia) or diabetes, continue to monitor your blood sugar as your doctor tells you to. Your doctor may need to change your diet or medicine to help control your blood sugar while you take ZOLINZA. Be sure to tell your doctor if you are unable to eat or drink normally due to nausea, vomiting or diarrhea.

What are the possible side effects of ZOLINZA?

ZOLINZA may cause **serious side effects**. Tell your doctor right away if you have any of the following symptoms:

- **Blood clots in the legs (deep vein thrombosis)**
  - sudden swelling in a leg
  - pain or tenderness in the leg. The pain may only be felt when standing or walking.
  - increased warmth in the area where the swelling is.
  - skin redness or change in skin color

- **Blood clots that travel to the lungs (pulmonary embolus)**
  - sudden sharp chest pain
  - shortness of breath
  - cough with bloody secretions
  - sweating
  - rapid pulse
  - fainting
  - feeling anxious

- **Dehydration** (loss of too much fluid from the body). This can happen if you are having nausea, vomiting or diarrhea and can not drink fluids well.

- **Low blood cell counts:** Your doctor will periodically do blood tests to check your blood counts.
  - **Low red blood cells.** Low red blood cells may make you feel tired and get tired easily. You may look pale, and feel short of breath.
  - **Low platelets.** Low platelets can cause unusual bleeding or bruising under the skin. Talk to your doctor right away if this happens.

- **High blood sugar** (blood glucose). If you have high blood sugar or diabetes, monitor your blood sugar frequently as directed by your doctor. Tell your doctor right away if your blood sugar is higher than normal.

- **Electrocardiogram abnormality.** An electrocardiogram, or EKG, is a test that records the electrical activity of your heart. Your doctor will check your blood electrolytes and electrocardiogram

periodically.

In addition, the most common side effects with ZOLINZA include:

- **Stomach and intestinal problems,** including diarrhea, nausea, vomiting, loss of appetite, constipation and weight loss
- **Tiredness**
- **Dizziness**
- **Headache**
- **Changes in the way things taste and dry mouth**
- **Muscle aches**
- **Hair loss**
- **Chills**
- **Fever**
- **Upper respiratory infection**
- **Cough**
- **Increase in blood creatinine**
- **Swelling in the foot, ankle and leg**
- **Itching**

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZOLINZA. For more information, ask your doctor or pharmacist.

General information about ZOLINZA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ZOLINZA for a condition for which it was not prescribed. Do not give ZOLINZA to other people, even if they have the same symptoms you have. It may harm them.

Keep ZOLINZA and all medicines out of the reach of children.

This leaflet summarizes the most important information about ZOLINZA. If you would like to know more information, talk to your doctor. You can ask your doctor or pharmacist for information about ZOLINZA that is written for health professionals.

What are the ingredients in ZOLINZA?

Active ingredient: vorinostat

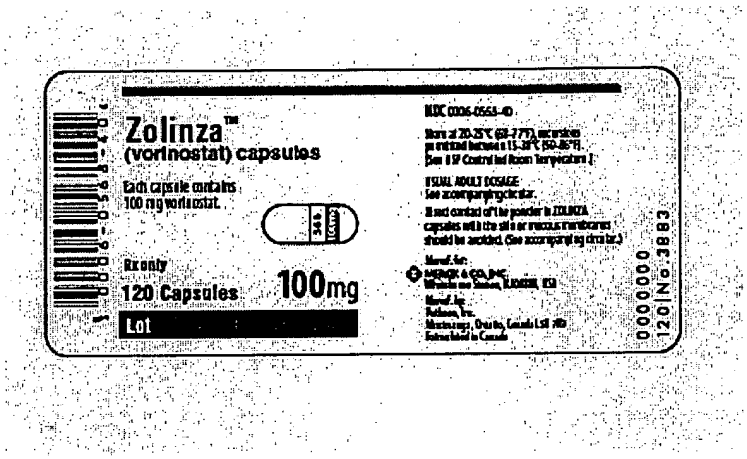
Inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The inactive ingredients in the capsule shell are titanium dioxide, gelatin, and sodium lauryl sulfate.

How should I store ZOLINZA?

Store ZOLINZA at room temperature, 68° F to 77° F (20° C to 25°C).

Issued: Month/year

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA


Zolinza™
(vorinostat) capsules
Each capsule contains
100 mg vorinostat.
MERCK
Rx only
120 Capsules
100mg
Lot
NDC 0006-0563-40
Store at 20-25°C (68-77°F), excursions
permitted between 15-30°C (59-86°F).
[See USP Controlled Room Temperature.]
USUAL ADULT DOSAGE.
See accompanying circular.
Manuf. for:
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
Manuf. for:
Patheon, Inc.
Mississauga, Ontario, Canada L5T 2B3
Rx Only
Printed in Canada
0000000
120 No. 3883

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 000000

1

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD MA 01742-9133

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
RE38,506	**$3,800.00**	**$0.00**	**10/004,411**	**11/29/94**	**10/04/91**	**12**	**NO**	**PAID**	**3254.1002-028**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Reg Number	File Date	Serial Number	Qualifier	Short Description	Long Description
58,915	9/2/1999	"0000"	Initial	Initial Investigational New Drug Application	
58,915	9/13/1999		Incoming Agency Correspondence	Acknowledgement letter of receipt	
58,915	9/21/1999		Incoming Agency Correspondence	Request for Information	FDA pharmacologist requests additional info regarding original IND.
58,915	9/24/1999	"0001"	Response to FDA Request for Information	Additional Information per Pharmacologist's Request (Faxes Dated 1999-Sep-21 and 1999-Sep-23)	
58,915	9/24/1999		Incoming Agency Correspondence	Identification of Clinical Hold Issue	FDA idenitifies "Clinical Hold issue", specifying Safety/Toxicology studies inadequate.
58,915	9/29/1999		Incoming Agency Correspondence	Safety/Toxicology clarification	FDA provides clarification on Safety/Toxicology studies required to support IND.
58,915	10/1/1999		Incoming Agency Correspondence	Preliminary notification of clinical hold	Via fax and telephone call, project manager provided preliminary notice of clinical hold for Safety/Toxicology reasons and conditions to allow daily x 5 study to proceed in humans. Medical Review deficiencies also specified.
58,915	10/1/1999		Other (specify in description)	Fax to FDA requesting clarification on FDA request	Fax request to FDA requesting clarification of what tissues represent "full panel of tissues" for histopathology studies.
58,915	10/4/1999		Incoming Agency Correspondence	FDA clarifies "full panel of tissues" for histopathology studies	
58,915	10/5/1999		Incoming Agency Correspondence	Fax of formal clinical hold letter signed by Division Director	Via fax, Project Manager provides the formal Clinical Hold letter (Dated Oct 05, 1999) signed by Dr. Pazdur, Division Director.
58,915	12/29/1999	"0002"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-059A (1)	
58,915	12/29/1999	"0002"	Information Amendment - Pharmacology/Toxicology	10 mg/ml 2 hour IV infusion via tail vein; 5 mg/ml administered via aural vein	
58,915	12/29/1999	"0002"	Response to FDA Request for Information	Revisions of original clinical protocol included in clinical hold letter from Richard Pazdur, M.D., dated October 5, 1999	
58,915	1/24/2000		Incoming Agency Correspondence	Official letter lifting Clinical Hold and allowing clinical trials to initiate.	
58,915	4/14/2000	"0003"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-059A(2)	
58,915	5/3/2000	"0004"	Information Amendment - Chemistry/Microbiology (CMC)	Additional Information for newly synthesized N-hydroxy-N'phenyl-octane-1, 8-diotic acid diamide (SAHA) and Certificates of Analysis	
58,915	7/14/2000	"0005"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(3)	

58,915	7/17/2000	"0006"	Information Amendment - Pharmacology/Toxicology	Summary Report Oral SAHA In Mice (Various Doses)	
58,915	7/31/2000	"0008"	Information Amendment - Chemistry/Microbiology (CMC)	Stability Study of N-hydroxy-N'phenyl-octane-1, 8-diotic acid diamide (SAHA)	
58,915	11/13/2000	"0009"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(4)	
58,915	11/17/2000	"0011"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(5)	
58,915	11/17/2000	"0010"	Information Amendment - Chemistry/Microbiology (CMC)	New Lot of N-hydroxy-N'phenyl-octane-1, 8-diotic acid diamide (SAHA) prepared by Southern Research	
58,915	2/1/2001	"0012"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(6)	
58,915	2/7/2001	"0013"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	ER # 939578
58,915	2/20/2001	"0014"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(7)	
58,915	4/4/2001		Incoming Agency Correspondence	Letter to remind MSK of its Annual IND progress report obligations	
58,915	4/24/2001	"0015"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	GL MRN 194020
58,915	4/24/2001	"0016"	Information Amendment - Chemistry/Microbiology (CMC)	Stability Study of N-hydroxy-N'phenyl-octane-1, 8-diotic acid diamide (SAHA)	
58,915	5/3/2001	"0017"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(8)	
58,915	5/17/2001		Other (specify in description)	Letter to FDA requesting opinion regarding sterility testing of final formulation	
58,915	5/21/2001	"0018"	Annual Report	Annual Report on Suberoylanilide Hydroxamic Acid / SAHA covering protocol #99-059 and #99-059A(1-7).	
58,915	6/5/2001	"0019"	Information Amendment - Chemistry/Microbiology (CMC)	Newly synthesized N-hydroxy-N'phenyl-octane-1, 8-diotic acid diamide (SAHA) prepared by ChemSyn Laboratories (Bulk Compound and Injectable Formulation)	
58,915	7/5/2001	"0020"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	MB MRN 665797
58,915	7/6/2001	"0021"	Protocol Amendment - New Protocol	MSK Protocol Number 01-021 - Advanced Malignancies Study	
58,915	7/6/2001	"0021"	Information Amendment - Chemistry/Microbiology (CMC)	New lot of N-hydroxy-N'phenyl-octane-1, 8-diotic acid diamide (SAHA) prepared by ChemSyn Laboratories (Lot #1136-1136-00-001, SAHA Capsules)	
58,915	7/6/2001	"0021"	Information Amendment - Pharmacology/Toxicology	Oral SAHA in mice treated once a day for 4-10 days	
58,915	7/11/2001		Incoming Agency Correspondence	Request for Information regarding pharmacology/toxicology	FDA pharmacology/toxicology reviewer requests submission of additional data relevant to submission dated July 06, 2001.
58,915	8/8/2001	"0022"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(9)	

58,915	8/29/2001	"0023"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	JK MRN 385706, DO MRN 003697
58,915	11/19/2001	"0025"	Protocol Amendment - Change in Protocol	MSK Protocol Number 99-59A(10)	
58,915	11/19/2001	"0024"	Protocol Amendment - Change in Protocol	MSK Protocol Number 01-021A(1) - Advanced Malignancies Study	
58,915	11/21/2001		Incoming Agency Correspondence	FDA provides sample language for transfer of IND responsibilities.	
58,915	12/20/2001	"0026"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	JK MRN 385706, DO MRN 003697
58,915	1/7/2002	"0027"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	DO MRN 003697
58,915	3/20/2002	"0028"	Annual Report	Annual Report covering protocols #99-059 and #01-021	
58,915	3/26/2002		Other (specify in description)	Letter from ATON to MSK Regarding IND Transfer	
58,915	3/27/2002	"0029"	Other/Transfer of Responsibility	Transfer of IND to Aton Pharma, Inc.	
58,915	3/28/2002	"0030"	Protocol Amendment - Change in Protocol	Adv. Malignancies Study #01-01A(2) (MSK #01-021) and Transfer of Obligation to CRO	
58,915	4/11/2002		Incoming Agency Correspondence	Transfer of Responsibility for IND to ATON is acknowledged by FDA.	Effective Transfer date: April 08, 2002.
58,915	4/17/2002	"0031"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	MSK-01-021-018/L-M
58,915	4/18/2002	"0032"	Information Amendment - Chemistry/Microbiology (CMC)	New Lot of Drug Substance (Aton Lot# A05-0203-001 or AMRI Lot# 1376-C-R0-01-42-04) prepared by Albany Molecular Research, Inc.	
58,915	4/23/2002	"0033"	Other (specify in description)	Initial Investigator's Brochure	
58,915	5/8/2002	"0034"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	MSK-01-021-020/G-K
58,915	5/16/2002	"0035"	Protocol Amendment - Change in Protocol	Adv. Malignancies Study #01-01A(3)	
58,915	5/30/2002	"0036"	Information Amendment - Chemistry/Microbiology (CMC)	Changes in Production of Intravenous Formulation of SAHA drug product (Aton Lot# B02-0201-001 or CBL Lot#1349-18)	
58,915	6/5/2002	"0037"	Information Amendment - Chemistry/Microbiology (CMC)	Production of 50 mg Capsules	
58,915	6/13/2002	"0038"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	MSK-01-021-023/C-C
58,915	7/3/2002	"0039"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	MSK-01-021-029/M-B
58,915	7/10/2002	"0040"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	MSK-01-021-023/C-C
58,915	7/22/2002	"0041"	Protocol Amendment - Change in Protocol	Adv. Malignancies Study #01-01A(4)	
58,915	8/30/2002	"0042"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	MSK-99-0059-023/B-E (or ATON 99-59A)
58,915	10/4/2002	"0043"	Protocol Amendment - New Protocol	02-01 (Adv. Head and Neck Malignancies); 02-02 (Unresponsive T-cell Lymphoma)	

58,915	10/7/2002	"0044"	Other (specify in description)	Revised Investigator's Brochure (Version 4 04-Oct-2002)	
58,915	11/14/2002	"0045"	Protocol Amendment - Change in Protocol	Adv. Malignancies Study #01-01A(5)	
58,915	11/25/2002	"0046"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient Number 002-001
58,915	12/9/2002	"0047"	Protocol Amendment - Change in Protocol	Adv. Head and Neck Malignancies Study #02-01A(1) and Unresponsive T-cell Lymphoma Study #02-02A(1)	
58,915	12/27/2002	"0048"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient Number 01-021-050/R-B
58,915	1/10/2003	"0049"	Protocol Amendment - Change in Protocol	Adv. Malignancies Study #01-01A(6)	
58,915	1/22/2003	"0050"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	0101A-004, 0101A-002, 0101A-001, 0202-001
58,915	2/20/2003	"0051"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient MSK 01-021-058
58,915	2/28/2003	"0052"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient MSK 01-021-043
58,915	3/24/2003	"0053"	Protocol Amendment - New Protocol	CL-01-03-01 - Advanced Leukemia Study	
58,915	4/7/2003	"0054"	Annual Report	Brief Summary of clinical, nonclinical, and CMC Issues from January 2002 to January 2003 in development of SAHA	
58,915	4/17/2003	"0055"	Other (specify in description)	Transfer of Obligations from Aton to Aton PharmaNet, Inc. (a CRO) for 01-01 and MSK 99-59	
58,915	4/30/2003	"0056"	Protocol Amendment - Change in Protocol	Adv. Malignancies Study #01-01A(7)	
58,915	5/13/2003	"0057"	Protocol Amendment - Change in Protocol	Advanced Leukemia Study CL-01-03-01(1)	
58,915	5/22/2003	"0058"	Other/Transfer of Responsibility	Elimination of Transfer of Clinical Trial Obligation to CRO in Serial 030 and 055	
58,915	6/6/2003	"0059"	General Correspondence	Change in Regulatory Affairs Contact for Aton Pharma, Inc. to Lorraine W. Sachs, M.S., RAC	
58,915	6/27/2003	"0061"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient MSK 01-021-0066/T-M
58,915	6/27/2003	"0060"	Information Amendment - Chemistry/Microbiology (CMC)	Change in Color of SAHA 50 mg capsule to white / dark brown	
58,915	6/30/2003	"0062"	Other/Meeting Information (other than Background Package)	Request for Type B EOP 2 Meeting - Clinical	
58,915	7/8/2003		Incoming Agency Correspondence	FDA grants ATON request for Clinical EOP2 meeting.	FDA grants ATON request for End of Phase II meeting (serial No. 062) for discussion of issues related to the clinical program. Meeting scheduled for September 09, 2003. Fax provides proposed list of FDA attendees and required information for the background package.

58,915	7/18/2003	"0063"	Other/Meeting Information (other than Background Package)	Request for Type B EOP 2 Meeting - CMC	
58,915	7/22/2003	"0064"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient MSK 01-067
58,915	7/25/2003		Incoming Agency Correspondence	SAHA approved by the DCTD Drug Development Group for further development	NSC 701852
58,915	7/28/2003		Incoming Agency Correspondence	FDA grants ATON request for CMC EOP2 meeting	FDA grants ATON request for End of Phase II meeting (serial No. 063) for discussion of issues related to CMC. Meeting scheduled for October 15, 2003. Fax provides proposed list of FDA attendees.
58,915	7/31/2003	"0066"	Protocol Amendment - Change in Protocol	Unresponsive T-cell Lymphoma Study #02-02A(2)	
58,915	7/31/2003	"0065"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0202-018
58,915	8/7/2003	"0067"	Other/Background Package	Information Package for EOP 2 Clinical meeting on September 9, 2003 from 2:00-3:00 pm	
58,915	8/11/2003	"0068"	Protocol Amendment - Change in Protocol	Adv. Leukemia Study CL-01-03-01(2)	
58,915	8/20/2003	"0069"	Protocol Amendment - Change in Protocol	Adv. Malignancies Study #01-01A(8)	
58,915	9/2/2003	"0070"	Protocol Amendment - New Protocol	03-02 - Advanced Multiple Myeloma Study	
58,915	9/3/2003		Incoming Agency Correspondence	FDA provides responses to ATON's EOP2 clinical.	FDA provides responses to ATON's questions (serial No. 062) submitted for EOP2 meeting scheduled for clinical program review on Sept 9, 2003.
58,915	9/12/2003	"0071"	Other/Background Package	Information Package for EOP 2 CMC meeting on October 15, 2003 from 2:00-3:00 pm	
58,915	9/16/2003	"0072"	Information Amendment - Pharmacology/Toxicology	See Long Description for Details	1. Aton Reference Number A-PTG-008 WIN 64652: Salmonella/ Mammalian-Microsome Preincubation Mutagenicity Assay(Ames Test) and Escherichia Coli WP2 uvrA Reverse Mutation Assay with a Confirmation Assay. 2. Aton Reference Number A-PTG-016 WIN 64652: In vivo Chromosome Aberraton Analysis of Chinese Hamster Ovary (CHO) Cells (Protocol 108).
58,915	9/16/2003	"0073"	Information Amendment - Clinical	Submission of Current CVs, 1572s, Financial Disclosures, and Licenses for Principal Investigators	
58,915	9/19/2003	"0074"	Information Amendment - Clinical	Revised Investigator's Brochure (Replaces Previous Edition dated 12-Sept-2003).	
58,915	9/24/2003		Incoming Agency Correspondence	FDA minutes from 09-Sep-03 EOP2 meeting	FDA meeting minutes for EOP2 meeting held on September 09 to discuss clinical program, 2003.

58,915	9/26/2003	"0075"	Other (specify in description)	Request for Fast Track Designation for the Indication of Cutaneous T-Cell Lymphoma	
58,915	10/3/2003	"0076"	Information Amendment - Pharmacology/Toxicology	See long description for details.	1. Aton Reference Number A-PTM-029: The Evaluation fo the Ability of AP390, AP660, and AP661 to Inhibit the Catalytic Acitivities of Selected Cytochrome P450 Isoenzymes. 2. Aton Reference Number A-PTM-023: In Vitro Evaluation of SAHA as an Inducer of CYP450 Expression.
58,915	10/6/2003		Incoming Agency Correspondence	FDA comments on the appropriateness of a volunteer study on food effects given the genotoxic status.	FDA comments from EOP2 meeting minutes (Action item #2) and in response to P. Andrews email of September 24, 2003.
58,915	10/7/2003	"0077"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0101-067
58,915	10/7/2003		Incoming Agency Correspondence	FDA provides responses to ATON's questions (serial No. 063) submitted for EOP2 meeting scheduled for CMC review on Oct 15, 2003.	FDA answers questions included in CMC EOP2 background package prior to EOP2 meeting scheduled for Oct 15, 2003.
58,915	10/10/2003	"0078"	Information Amendment - Pharmacology/Toxicology	See long description for details.	Single Dose: A-PTT-011, IV Mice; A-PTT-009,Acute IV Infusion, Mice; A-PTT-010, IV Rats; A-PTT-013, Four Hour IV Infusion, Female Beagle Dogs. Repeated Dose: A-PTT-038, Non-tumored Nude Mice; A-PTT-007, IV Infusion in Beagle Dogs; A-PTT-014, 120 hour IV Infusion. Special: A-PTZ-019, In Vitro on Dog Whole blood and Plasma; A-PTZ-020, In Vitro and Glycine Buffer, pH 11, on Dog Whole Blood and Plasma (Protocol 00387).
58,915	10/14/2003	"0079"	Other/Meeting Information (other than Background Package)	Request for type B EOP2 meeting - nonclinical	
58,915	10/16/2003	"0080"	Protocol Amendment - New Protocol	Adv. CTLC Study CL-01-0303 - Request for Special Protocol Assessment	
58,915	10/16/2003	"0081"	Information Amendment - Pharmacology/Toxicology	See long description for details.	Follow up from type B EOP2 meeting for SAHA for treatment of cutaneous T-Cell lymphoma and diffuse large B-cell lymphoma. Request concurrence of revised study planned to evaluate a single dose of SAHA in healthy volunteers.
58,915	10/23/2003		Incoming Agency Correspondence	FDA grants ATON's request (serial no. 079) for EOP2 meeting to review preclinical studies required to support the SAHA program	Preclinical EOP2 meeting scheduled for December 10, 2003. FDA provides list of proposed FDA attendees.
58,915	10/23/2003		Incoming Agency Correspondence	FDA meeting minutes for CMC EOP2 meeting.	
58,915	10/31/2003	"0082"	Information Amendment - Clinical	Financial Disclosure Statements from Clinical Investigators	

58,915	11/7/2003	"0083"	Other (specify in description)	Request for concurrence of photographic guidelines as discuessed in clinical EOP2 meeting	
58,915	11/7/2003	"0084"	Other/Background Package	Information package for EOP2 nonclinical meeting on December 10, 2003 at 3:30 pm	
58,915	11/7/2003	"0085"	Protocol Amendment - Change in Protocol	Unresponsive T-cell Lymphoma Study #02-02A(3)	
58,915	11/12/2003		Incoming Agency Correspondence	FDA responds to ATON questions (Serial No. 081) regarding a study in healthy volunteers	FDA approves proposed parallel study design and will not require additional PharmTox data. FDA does not approve a cross-over study design.
58,915	12/1/2003		Incoming Agency Correspondence	FDA responses to ATON Protocol CL-01-0303 (CTCL) Special Protocol Assessment request (serial no. 080)	letter received on 05-Dec-2003
58,915	12/3/2003	"0086"	Other/Meeting Information (other than Background Package)	Request for Clarification on Answers to Questions from Special Protocol Assessment for Protocol CL-01-0303	
58,915	12/3/2003		Incoming Agency Correspondence	FDA grants fast track status to SAHA for cutaneous T-cell Lymphoma (CTCL)	
58,915	12/4/2003		Incoming Agency Correspondence	FDA provides responses to ATON's questions (serial No. 079) submitted for EOP2 meeting scheduled for nonclinical review on Dec 10, 2003.	FDA answers questions included in Preclinical EOP2 background package prior to EOP2 meeting scheduled for Dec 10, 2003.
58,915	12/11/2003	"0087"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0101-067
58,915	12/12/2003	"0088"	Other/Meeting Information (other than Background Package)	Preread for Clarification on Answers to Questions from Special Protocol Assessment for Protocol CL-01-0303	
58,915	12/15/2003		Incoming Agency Correspondence	FDA confirms the type A meeting to review the protocol for special Assessment on January 05, 2004	ATON Protocol CL-01-3030 (CTCL) Special Protocol Assessment request (serial no. 080)
58,915	12/17/2003		Incoming Agency Correspondence	FDA meeting minutes for the EOP2 meeting for pharmacology/toxicology held on December 02, 2003.	
58,915	12/19/2003		Incoming Agency Correspondence	FDA Response to Aton's Request for Clarification to Agency's Special Protocol Assessment letter dated Dec. 01, 2003.	
58,915	12/23/2003	"0089"	Information Amendment - Chemistry/Microbiology (CMC)	Multiple changes in both drug substance and drug product sections	
58,915	12/23/2003	"0090"	Information Amendment - Pharmacology/Toxicology	Follow up from the Type B EOP2 meeting for the SAHA nonclinical program	
58,915	1/6/2004	"0091"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0101-064
58,915	1/16/2004	"0092"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0101-007
58,915	1/21/2004	"0093"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0101-025
58,915	2/2/2004	"0094"	Protocol Amendment - New Investigator	CL-01-0303 - Youn Kim, M.D.	
58,915	2/9/2004	"0095"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0101-058

58,915	2/11/2004	"0096"	Protocol Amendment - New Protocol	Effect of Food on Bioavailability of SAHA in Healthy Adult Volunteers #03-04	
58,915	3/2/2004	"0097"	Protocol Amendment - Change in Protocol	Adv. CTLC Study CL-01-0303 amendment 1	
58,915	4/1/2004	"0098"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (See Long Description for Report Numbers)	Patient 0301-120
58,915	4/13/2004	"0099"	Protocol Amendment - Change in Protocol	Unresponsive T-cell Lymphoma Study #02-02A(4)	
58,915	4/23/2004	"0100"	General Correspondence	Notification of MRL authority to submit directly to IND on behalf of ATON	
58,915	4/30/2004	"0101"	General Correspondence	Communication to FDA of Regulatory contact at Merck for SAHA	
58,915	5/4/2004	"0102"	General Correspondence	End of Phase II Clarification regarding adequate urinary elimination characterization	
58,915	5/25/2004	"0103"	Annual Report	Reporting Period: February 01, 2003-January 31, 2004	
58,915	5/28/2004	"0104"	Protocol Amendment - Change in Protocol	ATON PN CL-01-0303 amendment 2/Merck PN 001-02 Adv. CTCL Study	
58,915	6/21/2004	"0106"	Protocol Amendment - Change in Protocol	ATON PN CL-01-0301 amendment 3/Merck PN 003-03 Adv. Leukemia Study	
58,915	7/7/2004	"0107"	Protocol Amendment - New Protocol	PN 008-00 - L-001079038 PK/PD Study in Cancer Patients	PN 008-00 - A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of L-001079038 in Patients with Advanced Cancer
58,915	7/8/2004	"0108"	Information Amendment - Chemistry/Microbiology (CMC)	CMC amendment - McKesson as potential labeling facility	
58,915	7/15/2004	"0109"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	
58,915	7/28/2004	"0110"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0407USA00687
58,915	8/16/2004	"0111"	Protocol Amendment - New Investigator	Merck PN 001 / Aton CL-01-0303 (site 0008, Youn Kim, MD)	
58,915	8/25/2004	"0112"	Response to FDA Request for Information	Request for photographic samples and revised CRF for Aton PN CL-01-0303/Merck PN 001	Photographic samples and revised CRF for Aton PN CL-01-0303/Merck PN 001 as requested in an e-mail by FDA on December 19, 2003
58,915	9/2/2004	"0113"	Information Amendment - Chemistry/Microbiology (CMC)	CMC amendment: addition of Merck as manufacturing site, updated process and updated drug product	CMC amendment: includes updates to the information provided by ATON in S/N 089, dated December 23, 2003, such as the addition of Merck as a potential manufacturing, packaging and labeling facility pertaining to the drug products described in IND 58,915 which could be used in clinical studies planned for the near future. Additionally, updated drug product analytical methods and batch analysis are provided.
58,915	9/15/2004	"0114"	Protocol Amendment - New Investigator	Merck PN 001 - Foss and Kuzel	

58,915	9/29/2004	"0115"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0409USA01564
58,915	10/4/2004	"0116"	Information Amendment - Clinical	Data Analysis Plan - Merck PN 001-02/Aton CL-01-0303	
58,915	10/4/2004	"0117"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0409USA01611
58,915	10/7/2004	"0121"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0409USA01564
58,915	10/7/2004	"0119"	Protocol Amendment - New Protocol	PN 007-00 - A Continuation Clinical Trial of Oral L-001079038 in Advanced Cancers	
58,915	10/7/2004	"0120"	Protocol Amendment - New Protocol	PN 013-00 - L-001079038 in Relapsed DLBCL	PN 013-00 - A Phase II Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Patients With Relapsed Diffuse Large B-Cell Lymphoma (DLBCL)
58,915	10/7/2004	"0118"	Information Amendment - Clinical	Revised CIB (Edition 1, R 28-Sep-2004, version 4.5); first Merck version submitted to FDA	
58,915	10/8/2004	"0122"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0409USA01611
58,915	10/15/2004	"0123"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0409USA01611
58,915	10/18/2004	"0124"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0410USA00690
58,915	10/27/2004	"0125"	Protocol Amendment - New Investigator	Merck PN 001 (Aton CL-01-0303) - Horwitz and Kim	Steven Horwitz, site 001-0006 and Ellen Kim, site 001-0007
58,915	11/11/2004	"0126"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0410USA00690 0410USA02309
58,915	11/24/2004	"0127"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0411USA02906
58,915	11/30/2004	"0128"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0410USA02309
58,915	12/2/2004	"0129"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0410USA02309
58,915	12/15/2004	"0130"	Protocol Amendment - New Investigator	PN001 (Duvic, Heald, Olsen, Pacheco, Vonderheid); PN008 (Rubin)	
58,915	1/10/2005	"0131"	Other/Transfer of Responsibility	Transfer of responsibility to Dr. Randi Albin	Transfer of liaison responsibility to Randi Albin, Ph.D.
58,915	1/13/2005	"0132"	Protocol Amendment - New Investigator	PN001 (Heffernan, Parker, Korman); PN013 (Rifkin)	PN001 - Heffernan (001-0014), Parker (001-0015), Korman (001-0017); PN008 - Rifkin (013-0005)
58,915	1/17/2005	"0133"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0412BEL00027
58,915	1/18/2005	"0134"	Other/IND Reference Authorization	IND Reference Authorization (Non-Merck IND - TBD Sherry S. Ansher, PhD, NCI)	
58,915	1/27/2005	"0135"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0412BEL00027
58,915	1/31/2005	"0136"	Protocol Amendment - Change in Protocol	ATON PN CL-01-0301 amendment 4/Merck PN 003-04 Adv. Leukemia Study	

58,915	2/1/2005	"0137"	Other/IND Reference Authorization	IND Reference Authorization (Non-Merck IND - TBD Division of Cancer Treatment and Diagnosis, NC	The Division of Cancer Treatment and Diagnosis plans to investigate the use of Suberoylanilide Hydroxamic Acid (SAHA), L-001079038) in a number of studies under their own IND. SAHA, L-001079038 will be supplied by Merck and Co., Inc.
58,915	2/3/2005	"0138"	Protocol Amendment - New Investigator	PN001 (Breneman, Geskin); PN013 (Furman)	PN001 - Breneman (001-0013), Geskin (001-0021); PN013 - Furman (013-0003)
58,915	2/4/2005	"0139"	Information Amendment - Clinical	PN001 - Addition of site for Timothy M. Kuzel, site #001-0009	
58,915	2/8/2005	"0140"	Protocol Amendment - Change in Protocol	PN 004-02/ Aton CL-01-0302 amendment 2 - Advanced Multiple Myeloma study	PN 004-02 / Aton CL-01-0302 (2) - Phase I/II Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Patients with Advanced Multiple Myeloma
58,915	2/8/2005	"0141"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0411USA02906
58,915	2/14/2005	"0142"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0409USA01564
58,915	2/15/2005	"0143"	Protocol Amendment - Change in Protocol	PN 006-09/ATON PN CL-01-0101 amendment 9 - Advanced Malignancies Study	PN 006-09/ATON PN CL-01-0101 amendment 9 - Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid - SAHA In Patients With Advanced Solid Tumors And Hematologic Malignancies
58,915	2/24/2005	"0144"	Protocol Amendment - New Investigator	PN 008 - Eric Rubin, MD (site 008-0001)	
58,915	2/25/2005	"0146"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0409USA01564
58,915	2/25/2005	"0145"	Information Amendment - Chemistry/Microbiology (CMC)	CMC; update to manufacturing sites, increase in Mg stearate, DP specs, DP stability for 100mg	
58,915	3/2/2005	"0147"	Protocol Amendment - Change in Protocol	PN 013-01 - L-001079038 in Relapsed DLBCL	
58,915	3/9/2005	"0148"	Protocol Amendment - New Protocol	PN 012-01 - Phase I Advanced Solid Tumor Study	PN 012-01 - A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Pemetrexed and Cisplatin in Patients With Advanced Cancer
58,915	3/9/2005	"0149"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0502USA01135
58,915	3/15/2005	"0150"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02180
58,915	3/17/2005	"0151"	Protocol Amendment - New Investigator	PN001 (Kimball); PN013 (Hainsworth, Pecora)	PN001 - Kimball (001-0018); PN013 - Hainsworth (013-0004), Pecora (013-0018)
58,915	3/22/2005	"0152"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA00926
58,915	3/28/2005	"0153"	Protocol Amendment - Change in Protocol	PN 007-01 - A Continuation Clinical Trial of Oral L-001079038 in Advanced Cancers	
58,915	3/30/2005	"0154"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02180 0409USA01564

58,915	4/1/2005	"0156"	Annual Report	Capsules Annual Report for 01-Feb-04 to 31-Jan-05	
58,915	4/4/2005	"0155"	Information Amendment - Clinical	PN001 - Transfer of SPONSOR Obligations to McKesson Bioservices Corp. and Theradex Systems, Inc	
58,915	4/6/2005	"0158"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0409USA01564 0504USA00203
58,915	4/6/2005	"0157"	Other/IND Reference Authorization	IND Cross Reference Request - request to cross reference SAEs from DCTD NCI IND 71976	IND Cross Reference Request - request that any serious adverse experience reports received from the Division of Cancer Treatment and Diagnosis, National Cancer Institute, concerning their IND 71976 be cross-referenced to Merck IND 58915
58,915	4/8/2005	"0159"	Protocol Amendment - New Protocol	PN 014-00 - Phase III Advanced Mesothelioma Study	PN 014-00 - A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Patients With Advanced Malignant Pleural Mesothelioma Previously Treated With Systemic Chemotherapy
58,915	4/8/2005	"0160"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA00926
58,915	4/11/2005	"0161"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05219 0504USA00203
58,915	4/12/2005	"0162"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05221
58,915	4/13/2005	"0163"	Protocol Amendment - Change in Protocol	PN 008-01 - L-001079038 PK/PD Study in Cancer Patients	PN 008-01 - A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of L-001079038 in Patients With Advanced Cancer
58,915	4/14/2005	"0164"	Protocol Amendment - New Investigator	PN 013 - Al-Katib (013-0001), Bernstein (013-0009), Goy (013-0018 replacing Pecora)	
58,915	4/20/2005	"0165"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05221
58,915	4/25/2005	"0166"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05221
58,915	4/26/2005	"0167"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02177
58,915	4/29/2005	"0168"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0504USA03934
58,915	5/4/2005	"0169"	Protocol Amendment - Change in Protocol	PN 007-01 (R28-Apr-2005) - A Continuation Clinical Trial of Oral L-001079038 in Advanced Cancer	
58,915	5/6/2005	"0170"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0502USA01135
58,915	5/9/2005	"0171"	Protocol Amendment - New Investigator	PN 001 (Pinter-Brown); PN 013 (Cheson, Gregory)	PN 001 (Pinter-Brown, site 001-0020); PN 013 (Cheson, site 013-0007; Gregory, site 013-0015)

58,915	5/12/2005	"0172"	Protocol Amendment - New Protocol	PN 015-00 - Phase I Study of L-001079038 and Bortezomib in Multiple Myeloma	PN 015-00 - Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Bortezomib in Patients With Advanced Multiple Myeloma
58,915	5/12/2005	"0173"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0504USA03934
58,915	5/13/2005	"0174"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0505USA00663
58,915	5/17/2005	"0175"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0504USA02267
58,915	5/20/2005	"0176"	Information Amendment - Clinical	PN 001 - correspondence address change - Kimball, site 001-0018	
58,915	5/20/2005	"0178"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0504USA02267
58,915	5/23/2005	"0179"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02180
58,915	5/24/2005	"0177"	Information Amendment - Pharmacology/Toxicology	Subchronic toxicity studies; 10 reports	
58,915	5/25/2005	"0180"	General Correspondence	Notification of approval of generic name, vorinostat	
58,915	5/27/2005	"0182"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0505USA00663
58,915	5/31/2005	"0181"	Response to FDA Request for Information	Teaching set to train PN001 investigators in the CTCL assessment procedure (mSWAT)	Sample teaching set used to train PN001 investigators in the CTCL assessment procedure (mSWAT), as requested by the Agency in 19-Dec-2003 e-mail
58,915	6/9/2005	"0183"	Information Amendment - Pharmacology/Toxicology	Chronic toxicity studies; 3 reports	
58,915	6/10/2005	"0185"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02266
58,915	6/13/2005	"0184"	Protocol Amendment - New Investigator	PN 004 (Siegel); PN 012 (Sharma); PN013 (Fisher, Lucas)	PN 004 (Siegel, site 004-0014); PN 012 (Sharma, site 012-0004), PN 013 (Fisher, site 013-0002) (Lucas, site 013-0012)
58,915	6/13/2005	"0186"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05219
58,915	6/14/2005	"0187"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0504USA02267
58,915	6/16/2005	"0188"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0505BEL00032
58,915	6/17/2005	"0189"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0505BEL00032
58,915	6/29/2005	"0190"	Information Amendment - Clinical	PN 013 - Addition of site for Dr. Lucas, 013-0012	
58,915	6/30/2005	"0192"	General Correspondence	PN 014: summary of revisions that MRL has agreed to based on FDA review of PN014	includes e-mail correspondences (as attachment) with FDA regarding FDA comments of PN014 from the medical team, statistical review and QoL review, and MRL responses to these comments
58,915	6/30/2005	"0193"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02177

58,915	6/30/2005	"0191"	Information Amendment - Pharmacology/Toxicology	Acute toxicity studies; 3 reports	
58,915	7/1/2005	"0194"	Information Amendment - Clinical	Revised CIB (Edition 2, R 29-Jun-2005, version 6.1)	
58,915	7/7/2005	"0195"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02172
58,915	7/11/2005	"0196"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02266
58,915	7/13/2005	"0197"	Information Amendment - Clinical	Revised CIB (Edition 2, R 11-Jul-2005, Version 7.0) - update made to Appendix 1	
58,915	7/14/2005	"0198"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00014
58,915	7/18/2005	"0199"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05221
58,915	7/21/2005	"0200"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0504USA02267 0503USA05219
58,915	7/22/2005	"0201"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02177 0503USA05221 0507BEL00014
58,915	7/25/2005	"0202"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00010 0507BEL00014
58,915	7/28/2005	"0203"	Information Amendment - Pharmacology/Toxicology	Mutagenicity studies; 7 reports	
58,915	7/29/2005	"0204"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00014
58,915	8/2/2005	"0205"	Protocol Amendment - New Investigator	PN 004 (Chanan-Khan); PN 013 (Fayad, Shea); PN014 (Vogelzang)	PN 004 (Chanan-Khan, site 004-0015); PN 013 (Fayad, site 013-0011; Shea, site 013-0008); PN 014 (Vogelzang, site 014-0047)
58,915	8/4/2005	"0206"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00041
58,915	8/5/2005	"0207"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00010
58,915	8/8/2005	"0208"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00010
58,915	8/9/2005	"0209"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00041
58,915	8/16/2005	"0210"	Information Amendment - Pharmacology/Toxicology	Reproductive toxicity studies - 8 reports	
58,915	8/19/2005	"0211"	Protocol Amendment - Change in Protocol	PN 013-02 - Vorinostat in Relapsed DLBCL	PN 013-02 - A Phase II Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Patients With Relapsed Diffuse Large B-Cell Lymphoma (DLBCL)
58,915	8/19/2005	"0212"	Protocol Amendment - Change in Protocol	PN 014-01 - Phase III Advanced Mesothelioma Study	PN 014-01 - A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Patients With Advanced Malignant Pleural Mesothelioma Previously Treated With Systemic Chemotherapy

58,915	8/23/2005	"0214"	Information Amendment - Clinical	PN004 - David Siegel, site 004-0014, IRB address change	
58,915	8/23/2005	"0213"	Information Amendment - Chemistry/Microbiology (CMC)	Update to drug substance and drug product information	
58,915	8/24/2005	"0215"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0508USA02996 0507BEL00010
58,915	8/25/2005	"0216"	Protocol Amendment - Change in Protocol	PN 001-03 - Phase IIb Multicenter Clinical Trial of Oral SAHA in Advanced Cutaneous T-Cell Lymp	
58,915	8/31/2005	"0217"	Information Amendment - Pharmacology/Toxicology	Miscellaneous toxicity studies - 8 reports	
58,915	9/1/2005	"0218"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0508FRA00051
58,915	9/7/2005	"0219"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0508FRA00051
58,915	9/9/2005	"0220"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02186
58,915	9/12/2005	"0221"	Protocol Amendment - New Investigator	PN 004 (Beveridge); PN 012 (Blumenschein); PN 013 (DeVos); PN 015 (Hussein); PN 006 (Scher)	PN 004 (Beveridge, site 004-0004), PN 012 (Blumenschein, site 012-0001), PN 013 (DeVos, site 013-0010), PN 015 (Hussein, site 015-0002), PN 006 (change in PI from O'Connor to Scher at site 006-0001)
58,915	9/13/2005	"0222"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0508USA02996
58,915	9/14/2005	"0223"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02175 0403USA02187 0508FRA00051
58,915	9/15/2005	"0224"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00041 0503USA05221
58,915	9/16/2005	"0225"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02176
58,915	9/19/2005	"0226"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0508FRA00051
58,915	9/20/2005	"0227"	Other/Meeting Information (other than Background Package)	Pre-NDA (Type B) meeting request letter	
58,915	9/20/2005	"0228"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02175
58,915	9/21/2005	"0229"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02180
58,915	9/28/2005	"0231"	Information Amendment - Clinical	PN015 - transfer of obligations to PRA as CRO	
58,915	9/28/2005	"0232"	Information Amendment - Clinical	PN 012 - transfer of obligations for PRA as CRO	
58,915	9/28/2005	"0230"	Information Amendment - Clinical	PN 014 - transfer of obligations to PRA as CRO	
58,915	9/30/2005		Incoming Agency Correspondence	FDA response to pre-NDA meeting request - meeting to be held on December 5, 2005, 12-1 pm	
58,915	9/30/2005	"0233"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02176 0508FRA00051

58,915	10/6/2005	"0235"	Protocol Amendment - Change in Protocol	PN 012-02 - Phase I Advanced Solid Tumor Study	PN 012-02 - A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Pemetrexed and Cisplatin in Patients With Advanced Cancer
58,915	10/6/2005	"0234"	General Correspondence	Notification of change in compound ID to MK-0683	
58,915	10/7/2005	"0236"	Protocol Amendment - New Investigator	PN 006 (site 006-0001, addition of Krug as co-PI); PN 013 (site 013-0002, change to Jacobsen)	
58,915	10/7/2005	"0237"	Protocol Amendment - New Protocol	PN 025-00 - Vorinostat and Erlotinib Combo in Patients With Relapsed/Refractory NSCLC	PN 025-00 - A Phase I/II Clinical Trial of Oral Vorinostat (MK-0683) in Combination With Erlotinib in Patients With Relapsed/Refractory Non-Small-Cell Lung Cancer
58,915	10/10/2005	"0239"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05221
58,915	10/10/2005	"0238"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0501USA02912 0507USA00946 0510USA00516
58,915	10/11/2005	"0240"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0508FRA00051
58,915	10/12/2005	"0241"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0412BEL00027
58,915	10/13/2005	"0242"	Information Amendment - Chemistry/Microbiology (CMC)	CMC - allowance in minor variation in the coarse and fine DS ration in the manufacturing proces	
58,915	10/14/2005	"0243"	Information Amendment - Clinical	PN 001 - change in correspondence address for site 001-0020 (Pinter-Brown)	
58,915	10/17/2005	"0244"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05221 0508FRA00051
58,915	10/19/2005	"0245"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02175
58,915	10/21/2005	"0246"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0510USA00516 0507BEL00010 0403USA02182
58,915	10/24/2005	"0247"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02187
58,915	10/25/2005	"0248"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0510CHE00016 0508USA02686 0403USA02175 0403USA02184 0403USA02181
58,915	10/27/2005	"0249"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0505BEL00032 0507BEL00014 0510SWE00042
58,915	10/28/2005	"0248"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA02181 0403USA02184 0403USA02175 0508USA02686 0510CHE00016
58,915	10/28/2005	"0250"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02176
58,915	10/28/2005	"0251"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02182
58,915	11/1/2005	"0253"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0409USA01611

58,915	11/2/2005	"0254"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0507BEL00010
58,915	11/3/2005	"0255"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0403USA02312
58,915	11/4/2005	"0252"	Other/Background Package	Pre-NDA Meeting Background Package	
58,915	11/4/2005	"0256"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0503USA05221
58,915	11/8/2005	"0258"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0412BEL00027 0510CHE00016
58,915	11/8/2005	"0257"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0510SWE00042
58,915	11/14/2005	"0259"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0409USA01611
58,915	11/15/2005	"0260"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0510SWE00042
58,915	11/16/2005	"0261"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0409USA01564
58,915	11/17/2005	"0262"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0405USA02122 0504USA02267
21-991	12/6/2005		Original Application	Initial submission of NDA application: Nonclinical Section	Rolling Submission for Vorinostat Capsules for CTCL - Nonclinical Section
58,915	12/9/2005	"0263"	General Correspondence	MRL response to Agency comments regarding pre-NDA background package	
58,915	12/21/2005	"0264"	Protocol Amendment - New Investigator	PN 007, PN 014	PN 007 (Geskin, site 0003; Krug, site 0004; Sharma, site 0011; Rubin, site 0012); PN 014 (Sterman, site 0034; Conkling, site 0038; Kindler, site 0040; Krug, site 0041; Dudek, site 0044; Glenn, site 0051; Chu, site 0053; Ross, site 0063)
58,915	12/22/2005	"0265"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0512DEU00091
58,915	12/28/2005	"0266"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0512DEU00091
58,915	12/30/2005	"0267"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0512deu00091
58,915	1/5/2006	"0268"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0512gbr00087
58,915	1/10/2006	"0269"	Information Amendment - Clinical	PN 001 - change in correspondence address for site 001-0011 (Pacheco)	
58,915	1/10/2006	"0270"	Protocol Amendment - New Investigator	PN 007 (Parker); PN 012 (Sharma); PN 013 (Foran; Bociek); PN 025 (Sharma)	PN 007 (Parker, site 007-0008); PN 012 (Sharma, site 012-0004); PN013 (Foran, site 013-0019; Bociek, site 013-0027); PN 025 (Sharma, site 025-0003)
58,915	1/12/2006	"0271"	Other/IND Reference Authorization	IND Reference Authorization Letter - David R. Jones, MD	
58,915	1/13/2006	"0272"	Other/IND Reference Authorization	IND Reference Authorization Letter - Pamela N. Munster, MD	
58,915	1/13/2006	"0273"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0512DEU00091

58,915	1/18/2006	"0274"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0512GBR00087
58,915	1/19/2006	"0275"	General Correspondence	Response to DSI request from review of the pre-NDA background package	
58,915	1/25/2006	"0276"	Information Amendment - Clinical	PN 014 - Statistical Analysis Plan, version 3	
58,915	2/6/2006	"0277"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0510CHE00016
58,915	2/7/2006	"0278"	Information Amendment - Clinical	Change in correspondence/site address, site 014-0047 (Dr. Vogelzang)	
58,915	2/8/2006	"0279"	Protocol Amendment - New Investigator	PN 007, PN 014, PN 025	PN 007 (Duvic, site 007-0002; Korman, site 007-0005; Pacheco, site 007-0007); PN 014 (Belani, site 014-0029; Hausner, site 014-0030; Cameron, site 014-0037; Robert, site 014-0046; Feld, site 014-0054); PN 025 (Christiansen, site 025-0004)
58,915	2/9/2006	"0280"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0510CHE00016
58,915	2/16/2006	"0281"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0510CHE00016
21-991	2/22/2006		Original Application	Rolling Submission for Vorinostat Capsules for CTCL - CMC Section	Rolling Submission for Vorinostat Capsules for CTCL - CMC Section
58,915	3/3/2006	"0282"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0602USA05786
58,915	3/7/2006	"0284"	Protocol Amendment - New Investigator	PN 007, PN 012, PN 014, PN 015, PN 025	PN 007 (Breneman, site 007-0001; Pinter-Brown, site 007-0009; Vonderheid, site 007-0010); PN 012 (Robert, site 012-0006); 014 (Mekhail, site 014-0073); 015 (Jagannath, site 015-0001; Weber, site 015-0003; Singhal, site 015-0004); 025 (Schwartzberg, site 025-0006)
58,915	3/7/2006	"0283"	Protocol Amendment - Change in Protocol	PN 015-10 - Phase I Study of Vorinostat and Bortezomib in Multiple Myeloma	PN 015-10 - Phase I Clinical Trial of Oral Vorinostat (MK-0683) in Combination With Bortezomib in Patients With Advanced Multiple Myeloma
58,915	3/9/2006	"0285"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0602USA05786
58,915	3/13/2006	"0287"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0602USA05786
58,915	3/13/2006	"0286"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0511FRA00051
58,915	3/16/2006	"0288"	General Correspondence	Notification of Trademark	
58,915	3/20/2006	"0289"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	
58,915	3/28/2006	"0291"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0602USA05786
58,915	3/31/2006	"0290"	Annual Report	Capsules Annual Report for 01-Feb-2005 to 31-Jan-2006	
58,915	4/4/2006	"0292"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0603USA04615

21-991	4/5/2006		Original Application	Final submission of NDA: Clinical and Module 1 (completes NDA)	Rolling Submission for Vorinostat Capsules for CTCL - Clinical and Module 1 (completes NDA)
58,915	4/6/2006	"0293"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0603USA04615
21-991	4/7/2006		Other (specify in description)	Duplicate set of hard copy Module 1 docs in 05-Apr-2006 original application	
58,915	4/12/2006	"0295"	General Correspondence	Consolidation of FDA statistical comments to S/N 276 (PN 014 SAP) and MRL response	
58,915	4/19/2006	"0296"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0603USA04615
21-991	4/26/2006		Incoming Agency Correspondence	Fax providing a list of site specific data requested by DSI to facilitate/complete inspections	Fax from J. Lloyd Johnson (DSI, FDA) to R. Albin (MRL) that provided MRL with a listing of information requested of sponsors for submission to DSI to facilitate and allow for completion of required clinical data inspections for the NDA. The DSI also stated that an orientation of how the DSI site specific info is organized in the submission would be helpful.
21-991	4/28/2006		Other (specify in description)	Information regarding original hard copy debarment certification	
58,915	5/1/2006	"0298"	Safety Report – Initial Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0604USA02115
58,915	5/1/2006	"0297"	Other/IND Reference Authorization	IND Reference Authorization Letter - Sponsor Investigator Heinz-Josef Lenz	
58,915	5/3/2006	"0299"	Information Amendment - Clinical	PN 001 - change in correspondence address, site 001-0004 (Dr. Foss)	
58,915	5/3/2006	"0301"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0603USA04615
58,915	5/3/2006	"0300"	Protocol Amendment - New Investigator	PN 007 (Takimoto); PN 013 (OConnor)	PN 007 (Takimoto, site 007-0016); PN 013 (O'Connor, site 013-0016)
58,915	5/5/2006	"0302"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA02828
58,915	5/9/2006	"0303"	Protocol Amendment - New Investigator	Correction to S/N 300 - inclusion of CVs & 1572s for Takimoto (007-0016) and OConnor (013-0016)	
58,915	5/10/2006	"0304"	Information Amendment - Clinical	PN 015 - notification that MRL will no longer use PRA as CRO for this study	
58,915	5/15/2006	"0305"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA04192 0604USA02828 0604USA02115
58,915	5/16/2006	"0306"	Protocol Amendment - Change in Protocol	PN 003-05 - Advanced Leukemia Study	
58,915	5/17/2006	"0307"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA02115
58,915	5/18/2006	"0308"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0602USA05786
21-991	5/18/2006		Other/Meeting Information (other than Background Package)	Meeting minutes and slides from May 8, 2006 Briefing Meeting	

58,915	5/23/2006	"0310"	General Correspondence	Consolidation of FDA statistical comment to S/N 295 and MRL response	
58,915	5/23/2006	"0309"	Other/IND Reference Authorization	IND Reference Authorization Letter - Sponsor Investigator Bryan J. Schneider	
58,915	5/25/2006	"0311"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0603USA04615
58,915	5/30/2006	"0312"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0605USA03856
21-991	5/31/2006		Incoming Agency Correspondence	Completion of filing review: NDA is sufficiently complete to permit a substantive review	
58,915	6/2/2006	"0313"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA02828
58,915	6/6/2006	"0314"	Protocol Amendment - New Investigator	PN 014 (Kelly, Hassan, and Govindan); PN 025 (Kelly, Govindan, Brahmer, and Dees)	PN 014 (Kelly, site 014-0043; Hassan, site 014-0048; Govindan, site 014-0069); PN 025 (Kelly, site 025-0001; Govindan, site 025-0005; Brahmer, site 025-0007; Dees, site 025-0008)
58,915	6/6/2006	"0315"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA02115
58,915	6/9/2006	"0316"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA02115 0604USA04192
58,915	6/15/2006	"0294"	Safety Report – Follow-up to a Written Report	3500\CIOMS\VAERS form (see Long Description for report numbers)	0602USA05786
21-991	6/19/2006		Amendment to Pending Application	Amended repeat-dose toxicity report TT #04-5502	
58,915	6/20/2006	"0317"	Information Amendment - Pharmacology/Toxicology	Amended tox report TT #04-5502	Amended tox report TT #04-5502 to include tables containing the individual male and female rat bone marrow cytology data from the Week 14 necropsy that were inadvertently omitted from the original report
58,915	6/20/2006	"0319"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA04192 0606FRA00015
58,915	6/21/2006	"0320"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0606FRA00015
58,915	6/26/2006	"0321"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0605USA03856
21-991	6/28/2006		Amendment to Pending Application	Amended repeat-dose toxicity report TT #04-5502 to correct missing info on page 303	
21-991	6/28/2006		Other/Response to Request for Information	5 empty samples of 100 mg capsules and container closure system intended for marketing	
58,915	6/29/2006	"0322"	Information Amendment - Clinical	Revised CIB (Edition 3, R 23-Jun-2006)	
58,915	6/30/2006	"0323"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0603USA04615
21-991	6/30/2006		Amendment to Pending Application	Update response duration and time-to-progression results for PN 001	Additional follow-up efficacy results for 12/15 patients who continued to receive vorinostat treatment at the time of PN 001 closure on April 11, 2006

58,915	7/6/2006	"0324"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0604USA02115
21-991	7/6/2006		Incoming Agency Correspondence	FAX containing medical reviewer comments requesting recalculation of TTP & duration of OR data	
58,915	7/10/2006	"0325"	Protocol Amendment - New Investigator	PN 025 - Dr. Troy H. Guthrie, Jr., site 025-0010	
58,915	7/13/2006	"0326"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0606FRA00078
21-991	7/14/2006		Other/Response to Request for Information	Recalc time-to-progression and overall response for patients in Study 001 requested on 06Jul06	
21-991	7/14/2006		Other/Response to Request for Information	Dataset for Study 008 in .xpt format as requested by Clin Pharm reviewer on 10Jul06	Dataset for Study 008 in .xpt format as requested by Clin Pharm reviewer on 10Jul06
21-991	7/21/2006		Other/Response to Request for Information	Response to request from Clin Pharm reviewer on 18-Jul-2006	
58,915	7/26/2006	"0327"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0607USA02717
21-991	7/28/2006		Other/Response to Request for Information	Photos supporting updated response and progression status for patients in PN 001	Submission of photographs, as requested by the Clinical review team on 13-Jul-2006, to support the additional follow-up efficacy results for 12/15 patients in PN 001 that were provided to the Agency on 30-Jun-2006
58,915	8/2/2006	"0328"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0605USA03856
58,915	8/3/2006	"0329"	Information Amendment - Chemistry/Microbiology (CMC)	Updated DS/DP, DP section for Erlotinib, copy of LOA to x-reference OSI IND 53728 for Erlotinib	
58,915	8/3/2006	"0330"	Protocol Amendment - New Investigator	PN 007 (Robert, site 007-0014); PN 014 (Reaume, site 014-0065; Shin, site 014-0071)	
21-991	8/4/2006		Other/Safety Update Report (SUR)	Safety Update Report	Safety Update Report
21-991	8/8/2006		Other/Response to Request for Information	Response to request from Pharmacology Reviewer on 04-Aug-2006	
58,915	8/14/2006	"0331"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0607USA02717
58,915	8/21/2006	"0332"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0607USA02717
58,915	8/23/2006	"0333"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0608DEU00103
21-991	8/29/2006		Other/Response to Request for Information	Response to labeling comments regarding PLR received on August 23, 2006	
58,915	8/30/2006	"0334"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0608USA05849
58,915	8/30/2006	"0335"	General Correspondence	Letter to inform agency of DSMB recommendation to temporarily suspend accrual for PN 014	
58,915	8/30/2006	"0336"	General Correspondence	Letter to inform agency of decision to close PN 013 to new patient enrollment	

58,915	9/5/2006	"0337"	Protocol Amendment - Change in Protocol	PN 012-03 - Phase I Advanced Solid Tumor Study	PN 012-03 - A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (MK-0683) in Combination With Pemetrexed and Cisplatin in Patients With Advanced Cancer
58,915	9/6/2006	"0338"	General Correspondence	Letter to inform Agency that Aton is no longer a wholly owned subsidiary of Merck	
21-991	9/6/2006		Other/Response to Request for Information	Response to comment received on 28-Aug-2006 regarding pharmacologic classification	
58,915	9/7/2006	"0340"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0608DEU00103
58,915	9/7/2006	"0339"	Protocol Amendment - New Investigator	PN 007 (Blumenshein, Jacobsen); PN 025 change in PI (Manno)	PN 007 (Blumenshein, site 007-0015; Jacobsen, site 007-0017); PN 025 change in PI at site 025-0003 from Sharma to Manno
21-991	9/8/2006		Other/Response to Request for Information	Draft of the Highlights Data Elements Table in response to the Agency's comment on 23-Aug-2006	
58,915	9/12/2006	"0341"	Safety Report – Follow-up to a Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0608USA05849
21-991	9/13/2006		Other/Response to Request for Information	Response to additional comments regarding pharmacologic classification received on 8-Sep-2006	
21-991	9/18/2006		Other/Response to Request for Information	Response to comment regarding HDAC classification w/ regard to product label rec'd on 15-Sep-06	
58,915	9/19/2006	"0342"	Safety Report – Initial Written Report	3500/CIOMS/VAERS form (see Long Description for report numbers)	0607GBR00086
21-991	9/22/2006		Other/Response to Request for Information	Response to comments from Clinical Pharmacology review received on 18-Sep-2006	
21-991	9/25/2006		Other/Response to Request for Information	Response to general container label comments received on 20-Sep-2006	
58,915	9/26/2006	"0343"	Protocol Amendment - Change in Protocol	PN 025-10 - Phase I/II in Combination With Erlotinib in Patients With Relapsed/Refractory NSCLC	PN 025-10 - A Phase I/II Clinical Trial of Oral Vorinostat (MK-0683) in Combination With Erlotinib in Patients With Relapsed/Refractory Non-Small-Cell Lung Cancer
21-991	9/26/2006		Other/Response to Request for Information	Summary of preliminary histone acetylation data for study 008 as requested on 18-Sep-2006	
58,915	9/28/2006	"0344"	Protocol Amendment - Change in Protocol	PN 012-04 - Phase I Advanced Solid Tumor Study	PN 012-04 - A Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (MK-0683) in Combination With Pemetrexed and Cisplatin in Patients With Advanced Cancer
21-991	9/29/2006		Other/Response to Request for Information	Preliminary histone acetylation raw data for study 008 as requested on 27-Sep-2006	

21-991	10/2/2006		Other/Response to Request for Information	Response to chemistry comments received on 29-Sep-2006	
21-991	10/2/2006		Other/Response to Request for Information	Response to additional container label comments received on 27-Sep-2006	
21-991	10/4/2006		Other/Post Marketing Commitment	Phase 4 commitments, as requested via e-mail on 18-Sep-2006	
21-991	10/5/2006		Other/Response to Request for Information	Acceptable version (version 2) of the container label as requested via email on 04-Oct-2006	
21-991	10/6/2006		Incoming Agency Correspondence	Approval Letter - includes request for FPL and post-marketing commitments	
58,915	10/9/2006	"0345"	Protocol Amendment - Change in Protocol	PN 015-11 - Phase I Study of Vorinostat and Bortezomib in Multiple Myeloma	PN 015-11 - Phase I Clinical Trial of Oral Vorinostat (MK-0683) in Combination With Bortezomib in Patients With Advanced Multiple Myeloma
58,915	10/9/2006	"0346"	Protocol Amendment - New Investigator	PN 025 - Buddharaju (0011), Yee (0015), Chingos (0016); change from Sunil to Chen (0003)	
21-991	10/12/2006		Other/Response to Request for Information	SPL of PI/PPI (including HDLE table) as committed to by MRL in October 4, 2006 e-mail	
58,915	10/17/2006	"0348"	Information Amendment - Chemistry/Microbiology (CMC)	Addition of Drug Product Placebo Sections to support NCI study	
21-991	10/18/2006		Other (specify in description)	Requests pertaining to outstanding SPL coding issues	
21-991	10/19/2006		Other/FPL	Printed Package Insert (USPC/USPPI) and Container Labeling	
58,915	10/23/2006	"0350"	Other/Meeting Information (other than Background Package)	Request for Type B (End-of-Phase I) Meeting for NSCLC program	
58,915	10/30/2006	"0352"	Other/IND Reference Authorization	IND Reference Authorization Letter - Sponsor Investigator Milind Javle, MD	
58,915	11/3/2006	"0353"	Protocol Amendment - New Investigator	PN 015 - Ronald Sobecks, MD replaced Mohamad Hussein, MD at site 015-0002	
21-991	11/3/2006		Other/Patent Information	Updated patent information	
58,915	11/16/2006	"0355"	Other/Background Package	End of Phase I (Type B) Background Package for December 19th 2006 Meeting	